# Renal tubular acidosis

## FEATURES OF THE RENAL TUBULAR ACIDOSIS (RTA) SYNDROMES

| Feature | Proximal RTA | Classic Distal RTA | Hyperkalemic Distal RTA |
|---|---|---|---|
| Plasma bicarbonate ion concentration | 14–18 mEq/L | Variable, may be < 10 mEq/L | 15–20 mEq/L |
| Plasma chloride ion concentration | Increased | Increased | Increased |
| Plasma potassium ion concentration | Mildly decreased | Mildly to severely decreased | Mildly to severely increased |
| Plasma anion gap | Normal | Normal | Normal |
| Glomerular filtration rate | Normal or slightly decreased | Normal or slightly decreased | Normal to moderately decreased |
| Urine pH during acidosis | ≤5.5 | >6.0 | ≤5.5 |
| Urine pH after acid loading | ≤5.5 | >6.0 | ≤5.5 |
| U-B $PCO_2$ in alkaline urine | Normal | Decreased | Decreased |
| Fractional excretion of $HCO_3^-$ at normal $[HCO_3^-]_p$ | >15% | <5% | <5% |
| Tm $HCO_3^-$ | Decreased | Normal | Normal |
| Nephrolithiasis | Absent | Present | Absent |
| Nephrocalcinosis | Absent | Present | Absent |
| Osteomalacia | Present | Present | Absent |
| Fanconi's syndrome* | Usually present | Absent | Absent |
| Alkali therapy | High dose | Low dose | Low dose |

Tm $HCO_3^-$—maximum reabsorption of bicarbonate; U-B $PCO_2$—difference between partial pressure of carbon dioxide values in urine and arterial blood.

*This syndrome signifies generalized proximal tubule dysfunction and is characterized by impaired reabsorption of glucose, amino acids, phosphate, and urate.

**FIGURE 6-25**

Renal tubular acidosis (RTA) defines a group of disorders in which tubular hydrogen ion secretion is impaired out of proportion to any reduction in the glomerular filtration rate. These disorders are characterized by normal anion gap (hyperchloremic) metabolic acidosis. The defects responsible for impaired acidification give rise to three distinct syndromes known as proximal RTA (type 2), classic distal RTA (type 1), and hyperkalemic distal RTA (type 4).

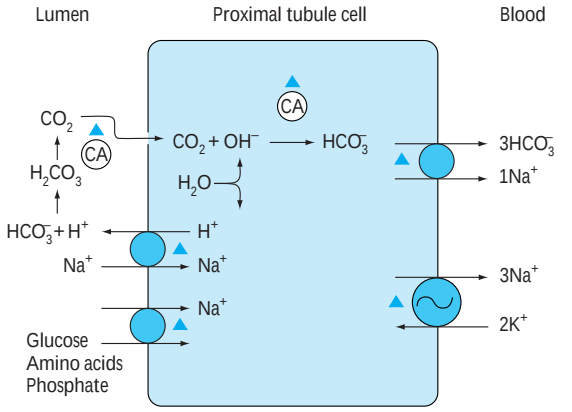


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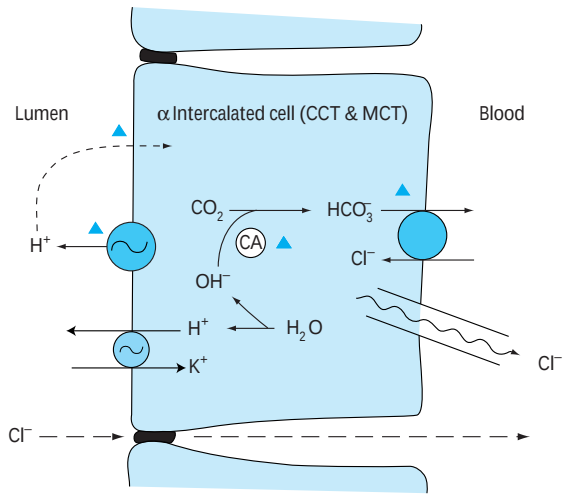
**FIGURE 6-26**

**A** and **B**, Potential defects and causes of proximal renal tubular acidosis (RTA) (type 2). Excluding the case of carbonic anhydrase inhibitors, the nature of the acidification defect responsible for bicarbonate ($HCO_3$) wastage remains unknown. It might represent defects in the luminal sodium ion– hydrogen ion ($Na^+$-$H^+$) exchanger, basolateral $Na^+$-$3HCO_3^-$ cotransporter, or carbonic anhydrase activity. Most patients with proximal RTA have additional defects in proximal tubule function (Fanconi's syndrome); this generalized proximal tubule dysfunction might reflect a defect in the basolateral $Na^+$-$K^+$ adenosine triphosphatase. $K^+$—potassium ion; CA—carbonic anhydrase. Causes of proximal renal tubular acidosis (RTA) (type 2). An idiopathic form and cystinosis are the most common causes of proximal RTA in children. In adults, multiple myeloma and carbonic anhydrase inhibitors (*eg*, acetazolamide) are the major causes. Ifosfamide is an increasingly common cause of the disorder in both age groups.

## B. CAUSES OF PROXIMAL RENAL TUBULAR ACIDOSIS

- Selective defect (isolated bicarbonate wasting)
  - Primary (no obvious associated disease)
    - Genetically transmitted
    - Transient (infants)
  - Due to altered carbonic anhydrase activity
    - Acetazolamide
    - Sulfanilamide
    - Mafenide acetate
    - Genetically transmitted
    - Idiopathic
    - Osteopetrosis with carbonic anhydrase II deficiency
    - York-Yendt syndrome
- Generalized defect (associated with multiple dysfunctions of the proximal tubule)
  - Primary (no obvious associated disease)
    - Sporadic
    - Genetically transmitted
  - Genetically transmitted systemic disease
    - Tyrosinemia
    - Wilson's disease
    - Lowe syndrome
    - Hereditary fructose intolerance (during administration of fructose)
    - Cystinosis
    - Pyruvate carboxylate deficiency
    - Metachromatic leukodystrophy
    - Methylmalonic acidemia
- Conditions associated with chronic hypocalcemia and secondary hyperparathyroidism
  - Vitamin D deficiency or resistance
  - Vitamin D dependence
- Dysproteinemic states
  - Multiple myeloma
  - Monoclonal gammopathy
- Drug- or toxin-induced
  - Outdated tetracycline
  - 3-Methylchromone
  - Streptozotocin
  - Lead
  - Mercury
  - Arginine
  - Valproic acid
  - Gentamicin
  - Ifosfamide
- Tubulointerstitial diseases
  - Renal transplantation
  - Sjögren's syndrome
  - Medullary cystic disease
- Other renal diseases
  - Nephrotic syndrome
  - Amyloidosis
- Miscellaneous
  - Paroxysmal nocturnal hemoglobinuria
  - Hyperparathyroidism




▲ Indicates possible cellular mechanisms responsible for Type 1 distal RTA

A

## B. CAUSES OF CLASSIC DISTAL RENAL TUBULAR ACIDOSIS

Primary (no obvious associated disease)
- Sporadic
- Genetically transmitted

Autoimmune disorders
- Hypergammaglobulinemia
- Hyperglobulinemic purpura
- Cryoglobulinemia
- Familial
- Sjögren's syndrome
- Thyroiditis
- Pulmonary fibrosis
- Chronic active hepatitis
- Primary biliary cirrhosis
- Systemic lupus erythematosus
- Vasculitis

Genetically transmitted systemic disease
- Ehlers-Danlos syndrome
- Hereditary elliptocytosis
- Sickle cell anemia
- Marfan syndrome
- Carbonic anhydrase I deficiency or alteration
- Osteopetrosis with carbonic anhydrase II deficiency
- Medullary cystic disease
- Neuroaxonal dystrophy

Disorders associated with nephrocalcinosis
- Primary or familial hyperparathyroidism
- Vitamin D intoxication
- Milk-alkali syndrome
- Hyperthyroidism
- Idiopathic hypercalciuria
  - Genetically transmitted
  - Sporadic
- Hereditary fructose intolerance (after chronic fructose ingestion)
- Medullary sponge kidney
- Fabry's disease
- Wilson's disease

Drug- or toxin-induced
- Amphotericin B
- Toluene
- Analgesics
- Lithium
- Cyclamate
- Balkan nephropathy

Tubulointerstitial diseases
- Chronic pyelonephritis
- Obstructive uropathy
- Renal transplantation
- Leprosy
- Hyperoxaluria

**FIGURE 6-27**

**A** and **B**, Potential defects and causes of classic distal renal tubular acidosis (RTA) (type 1). Potential cellular defects underlying classic distal RTA include a faulty luminal hydrogen ion–adenosine triphosphatase ($H^+$ pump failure or secretory defect), an abnormality in the basolateral bicarbonate ion–chloride ion exchanger, inadequacy of carbonic anhydrase activity, or an increase in the luminal membrane permeability for hydrogen ions (backleak of protons or permeability defect). Most of the causes of classic distal RTA likely reflect a secretory defect, whereas amphotericin B is the only established cause of a permeability defect. The hereditary form is the most common cause of this disorder in children. Major causes in adults include autoimmune disorders (*eg*, Sjögren's syndrome) and hypercalciuria [19]. CA—carbonic anhydrase.