



Pathophysiology of Renal Tubular Acidosis: Core Curriculum 2016

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Metabolic acidosis results from either the gain of an acid or the loss of a base. The former is due to exogenous or endogenous acid loads resulting in anion gap metabolic acidosis. The latter is due to the loss of a base from either the gastrointestinal or genitourinary tract, producing nonanion gap or hyperchloremic metabolic acidosis.

Renal tubular acidosis (RTA) arises from the kidney's inability to excrete enough acid or retain enough bicarbonate (HCO_3^-), resulting in a clinical syndrome characterized by nongap metabolic acidosis, hyperchloremia, and impaired urinary acidification. In this Core Curriculum, we briefly summarize the role of the kidney in acid-base homeostasis and discuss clinical presentations, diagnoses, and treatments of RTA.

OVERVIEW OF RENAL ACID-BASE HOMEOSTASIS

Total-Body Acid-Base Homeostasis

Metabolism of food particles generates both volatile carbonic acid, which is excreted by the lung, and fixed acid, which is generated primarily from metabolism of proteins. On a Western diet containing high levels of animal protein, an adult generates 15,000 mEq of volatile acid derived from fat and carbohydrate combustion and ~ 1 mEq of fixed acid per kilogram of body weight from metabolism of proteins. This latter is initially neutralized by the body buffers, including HCO_3^- , and then excreted by the kidney. The kidney is therefore responsible for the regeneration of lost buffers through excretion of 1 mEq of hydrogen ion (H^+) per kilogram of body weight on a daily basis. It maintains acid-base balance

by the reabsorption of all filtered HCO_3^- and the regeneration of HCO_3^- lost through metabolism of food particles. Both processes involve secretion of H^+ , initially to reabsorb filtered HCO_3^- and then to generate new HCO_3^- . The secreted H^+ would either combine with filtered HCO_3^- , resulting in HCO_3^- reabsorption, or combine with urinary buffers in the tubular fluid to be excreted as titratable acids and ammonium ion (NH_4^+), thus leading to HCO_3^- regeneration. Net acid excretion (NAE) by the kidney equals the sum of titratable acids and ammonium amounts minus the amount of HCO_3^- :

$$\text{NAE} = \text{titratable acids} + \text{NH}_4^+ - \text{HCO}_3^-$$

The amount of titratable acid is fixed and primarily reflects the amount of phosphate in urine. In contrast, the amount of NH_4^+ produced by the kidney varies greatly, increasing dramatically in acidemic states. Because the amount of titratable acid is fixed, a decrease in NAE is primarily due to either a decrease in NH_4^+ excretion or HCO_3^- loss (see details further in Curriculum).

Acid-Base Regulation by the Proximal Tubule

Total filtered HCO_3^- per day is equal to the plasma HCO_3^- concentration (24–26 mEq/L) multiplied by glomerular filtration rate (180–200 L/d) and is estimated to be approximately 4,000 to 5,000 mEq/d. Approximately 85% to 90% of filtered HCO_3^- is reabsorbed in the proximal tubule, with the rest being reabsorbed by the thick ascending limb of the loop of Henle, distal tubule, and collecting ducts. Reabsorption of HCO_3^- in the proximal tubule involves H^+ secretion primarily by the sodium ion (Na^+)/ H^+ exchanger isoform 3 (NHE3) and the H^+ -transporting adenosine triphosphatase (H^+ -ATPase). The secreted H^+ reacts with the luminal HCO_3^- to form carbonic acid, which rapidly dissociates to carbon dioxide, oxygen, and water. This latter reaction is catalyzed by luminal membrane carbonic anhydrase (CAIV). Carbon dioxide generated by this reaction freely enters proximal tubule cells and reacts with water to form carbonic acid, a reaction catalyzed by cytosolic carbonic anhydrase (CAII). Carbonic acid then dissociates rapidly to form HCO_3^- and H^+ . HCO_3^- exits through the basolateral membrane by the sodium bicarbonate cotransporter (NBCE1), and H^+ is again available to be secreted into the tubular lumen. The schematic in Fig 1 depicts the role of apical NHE3

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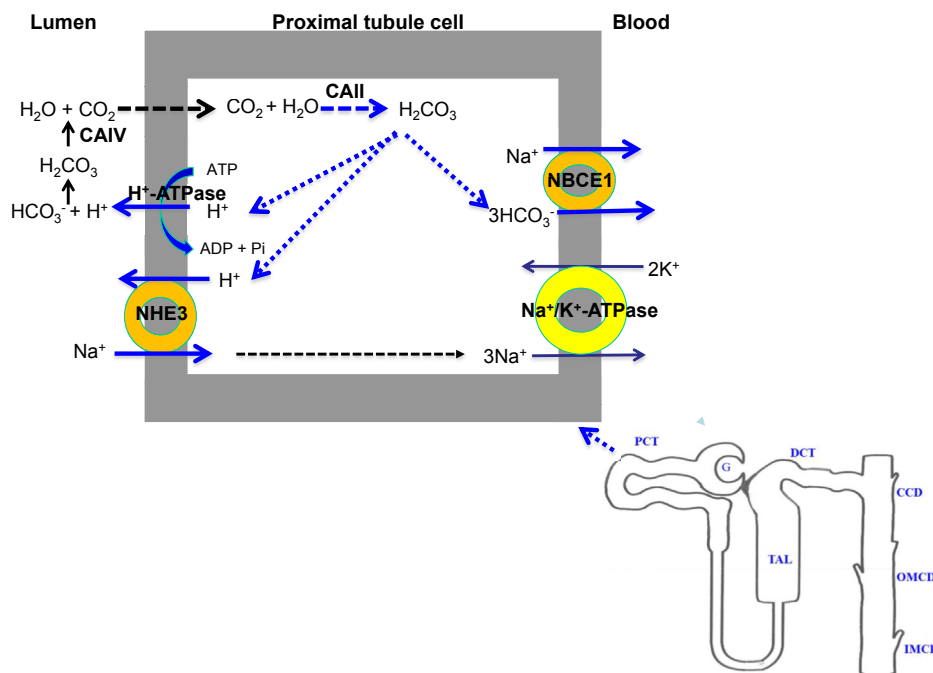


Figure 1. A schematic of the roles of acid-base transporters and carbonic anhydrases in acid (hydrogen ion [H^+]) secretion and bicarbonate (HCO_3^-) reabsorption in the kidney proximal tubule. Sodium ion (Na^+)/ H^+ exchanger isoform 3 (NHE3) and H^+ -transporting adenosine triphosphatase (H^+ -ATPase) are expressed on the apical membrane, whereas the sodium bicarbonate cotransporter (NBCE1) is located on the basolateral membrane of the proximal tubule. Carbonic anhydrase IV (CAIV) and CAII are detected on the apical membrane and in the cytoplasm, respectively. Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CCD, cortical collecting duct; DCT, distal convoluted tubule; IMCD, inner medulla collecting duct; K^+ , potassium ion; OMCD, outer medulla collecting duct; PCT, proximal convoluted tubule; Pi, inorganic phosphate; TAL, thick ascending limb.

and H^+ -ATPase, basolateral NBCE1, and membrane and cytoplasmic carbonic anhydrases in acid (H^+) secretion and HCO_3^- reabsorption in the kidney proximal tubule.

Acid-Base Regulation in the Distal Nephron (Collecting Duct)

The collecting duct has a main role in systemic acid-base homeostasis by fine-tuning acid and base excretion. The cortical collecting duct expresses 3 distinct cell types: A-intercalated cells, which secrete H^+ (acid); B-intercalated cells, which secrete HCO_3^- (base); and principal cells, which reabsorb Na^+ and water and secrete potassium ion (K^+). A-intercalated cells secrete acid (H^+) primarily by apical H^+ -ATPases (and H^+/K^+ -ATPases), generating new HCO_3^- under the control of cytosolic CAII. The generated HCO_3^- is transported to the blood in exchange for chloride ions (Cl^-) by the basolateral Cl^-/HCO_3^- exchangers, including the kidney anion exchanger 1 (AE1). Contrary to A-intercalated cells, which are detected along the length of the cortical and medullary collecting ducts, B-intercalated cells are predominantly detected in the cortical collecting duct and are almost absent in the medullary collecting duct. B-intercalated cells secrete HCO_3^- into the cortical collecting duct lumen in exchange for the

luminal Cl^- , primarily by the apical Cl^-/HCO_3^- exchanger pendrin. The intracellular acid generated subsequent to HCO_3^- secretion in B-intercalated cells is transported into blood membrane by the basolateral H^+ -ATPase.

Secreted H^+ by A-intercalated cells is buffered by titratable acids (mainly phosphate) and ammonia (NH_3 ; to generate NH_4^+), matching daily acid production. Although the amount of urinary phosphate is fixed, urinary NH_4^+ level varies because it is stimulated by systemic acidemia (and hypokalemia). H^+ secretion by H^+ -ATPase is modulated by the activity of the epithelial sodium channel (ENaC) in principal cells and by angiotensin II, aldosterone, and the calcium sensing receptor. Aldosterone plays a key role in H^+ secretion by stimulating ENaC and H^+ -ATPase. Aldosterone deficiency is characterized by sodium wasting, hyperkalemia, and RTA (see Hyperkalemic RTA section). The schematic in Fig 2 shows the localization of acid-base transporters and CAII in the cortical collecting duct and their role in acid-base transport.

Physiology of Ammoniogenesis and HCO_3^- Regeneration

NH_3 generates in the proximal tubule from metabolism of glutamine through the process of ammoniogenesis.

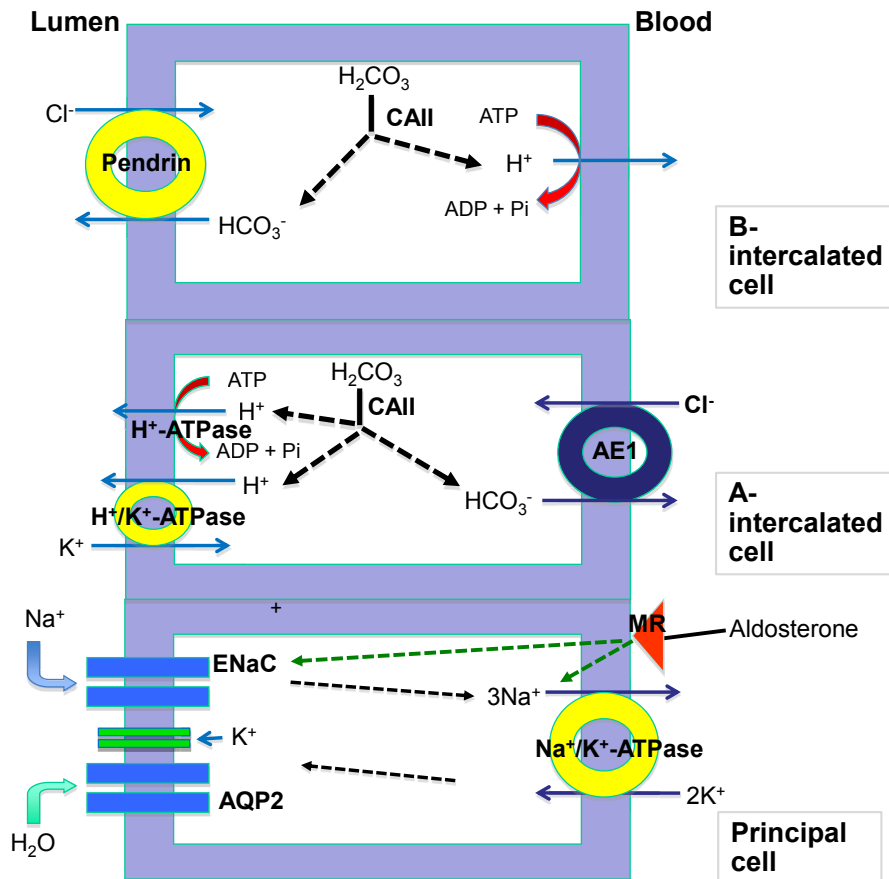


Figure 2. A schematic depicting localization of acid-base transporters and carbonic anhydrase II (CAII) in the cortical collecting duct (CCD) and their role in acid-base transport. Hydrogen ion (H^+)-transporting adenosine triphosphatase (H^+ -ATPase) and H^+/K^+ -ATPase are expressed on the apical membrane of A-intercalated cells and mediate H^+ secretion into the lumen, whereas the $\text{Cl}^-/\text{HCO}_3^-$ exchanger AE1 is located on the basolateral membrane of A-intercalated cells and facilitates the transport of bicarbonate (HCO_3^-) to the blood. The apical $\text{Cl}^-/\text{HCO}_3^-$ exchanger pendrin is located on the apical membrane of non-A-intercalated cells and facilitates HCO_3^- secretion into the lumen of the CCD in exchange for Cl^- absorption. Sodium ion (Na^+) and water are absorbed by the epithelial sodium channel (ENaC) and aquaporin 2 (AQP2), respectively, in principal cells. Abbreviations: Pi, inorganic phosphate; MR, mineralcorticoid receptor.

The NH_3 thus generated is secreted into the proximal tubule lumen, where it combines with H^+ (secreted by H^+ -ATPase) or is transported by the NHE3, which can function as an $\text{Na}^+/\text{NH}_4^+$ exchanger. Ammoniogenesis is regulated by intracellular pH (and indirectly by intracellular K^+). NH_4^+ is transported along the length of the proximal tubule to the medullary thick ascending limb, where it is absorbed into the medullary interstitium primarily by the apical $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter. Then the NH_3 is secreted into the collecting duct lumen, where it is trapped as NH_4^+ by H^+ secreted through intercalated cells by H^+ -ATPase (and H^+/K^+ -ATPase). Collecting duct NH_4^+ excretion requires the presence of Rhesus protein, RhCG, which is detected on both the apical and basolateral membrane of most cells of the distal convoluted tubule and intercalated cells of the connecting tubule and collecting duct. It is believed that under normal circumstances, RhCG is the key putative NH_3 transporter expressed in the human kidney and RhBG is expressed at below detectable levels. NH_4^+ excretion by the kidney results in elimination of acid in the collecting duct and generation of new HCO_3^- in the proximal tubule. Aldosterone plays a major role in NH_3 generation both through regulation of K^+ homeostasis and H^+ secretion into the lumen

of the collecting duct. The schematic in Fig 3 shows NH_4^+ generation and excretion in kidney tubules and their impact on HCO_3^- generation and acid elimination.

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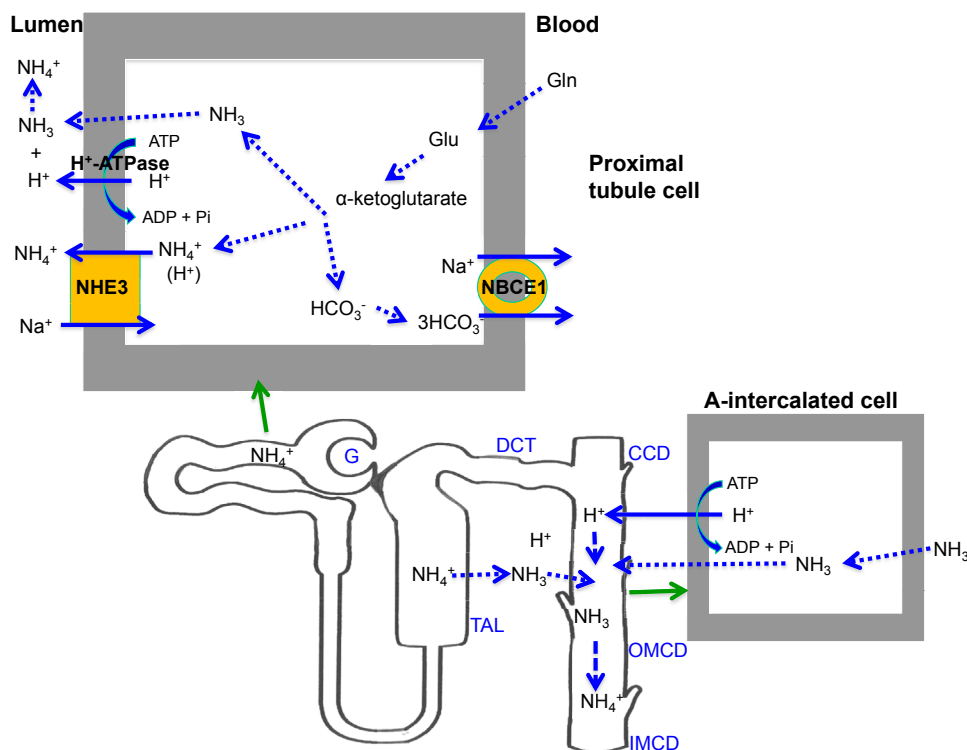


Figure 3. Generation and excretion of ammonium ion (NH_4^+) in kidney tubules and their impact on bicarbonate (HCO_3^-) generation and acid elimination. NH_4^+ is primarily generated in the proximal tubule consequent to the metabolism of glutamine. NH_4^+ transport along the length of the nephron, its absorption in the thick ascending limb, and its secretion into the collecting duct are shown. Abbreviations: CCD, cortical collecting duct; DCT, distal convoluted tubule; G, glomerulus; Gln, glutamine; Glu, glutamate; IMCD, inner medulla collecting duct; NBCE1, sodium bicarbonate cotransporter; OMCD, outer medulla collecting duct; TAL, thick ascending limb.

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RENAL TUBULAR ACIDOSIS

Based on clinical presentation and pathophysiologic mechanism, RTA is classified into proximal (pRTA or type II), distal (dRTA or type I), and hyperkalemic (or type IV) RTA (RTA type III [ie, combined pRTA and dRTA] is not detailed in this Curriculum because of its rarity).

Proximal RTA

pRTA is caused by defective HCO_3^- reabsorption in the proximal tubule (Figs 1 and 3). This could be due to defects in H^+ secretion by NHE3 or H^+ -ATPase, impairment of luminal or cytosolic

carbonic anhydrase, or defects in the exit of HCO_3^- by the $\text{Na}^+/\text{HCO}_3^-$ cotransporter NBCE1. pRTA could also present as a component of Fanconi syndrome due to generalized impairment of solute reabsorption in the proximal tubule, manifesting as renal loss of glucose, amino acids, phosphate, uric acid, and other organic anions.

Classification of pRTA

pRTA can present in hereditary or acquired forms.

Hereditary pRTA. Hereditary pRTA may manifest as autosomal recessive, autosomal dominant, or sporadic forms. Patients with autosomal recessive pRTA present with short stature, cataracts, and central nervous system calcification, and the condition is linked to mutations in the $\text{Na}^+/\text{HCO}_3^-$ cotransporter NBCE1 (Fig 1). In severe forms of pRTA, serum HCO_3^- concentrations < 10 mEq/L and blood pH < 7.1 have been reported. Although inactivation of NHE3 could result in HCO_3^- wasting and pRTA in animal models, mutations in NHE3 causing pRTA in humans have not been reported. Mutations in CAII lead to recessive mixed pRTA and dRTA, or type III RTA, with a predominance of distal acidification defect. Patients with CAII mutations present with HCO_3^- wasting, inability to lower urine pH to < 5.5 ,

and decreased NH_4^+ excretion. The gene(s) involved in autosomal dominant pRTA has (have) not yet been identified. The most common forms of familial Fanconi syndrome are due to cystinosis and Wilson disease. Other inherited causes of pRTA include:

- Lowe syndrome (oculocerebrorenal syndrome [OCRL]), an X-linked disorder characterized by cataract, mental retardation, and Fanconi-like pRTA, results from mutations in the *OCRL* gene, encoding α -phosphatidylinositol (4,5)-biphosphate phosphatase (PIP2P);
- Fanconi-Bickel syndrome, an autosomal recessive disorder characterized by pRTA and impaired utilization of glucose and galactose, is due to defects in monosaccharide transport across the tubular membranes; and
- Dent disease, an X-linked recessive disorder characterized by low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, and nephrolithiasis, results from mutations in either the chloride channel gene *CLCN5* or the *OCRL* gene.

Acquired pRTA. Most common causes include tubular injury by light chains, amyloidosis, multiple myeloma, autoimmune disorders, toxins such as cadmium or lead, and drugs, including ifosfamide, valproic acid, carbonic anhydrase inhibitors, and various antiretrovirals such as tenofovir (especially when administered to patients with human immunodeficiency virus [HIV] infection who are concomitantly receiving protease inhibitors such as ritonavir or reverse transcriptase inhibitors such as didanosine). Acquired pRTA may present as Fanconi syndrome, characterized by glycosuria, aminoaciduria, phosphaturia, and uricosuria.

Clinical Presentation and Diagnosis of pRTA. Patients with pRTA can be asymptomatic or could present with weakness/paralysis due to severe hypokalemia and, in rare cases, with bone pain/fracture due to osteomalacia. Hyperchloremic metabolic acidosis in pRTA tends to be milder because distal HCO_3^- reclamation is intact and bicarbonaturia disappears when HCO_3^- load falls below the HCO_3^- tubular maximum (often at serum HCO_3^- level of 14–18 mEq/L).

The key laboratory finding is the presence of hyperchloremic metabolic acidosis with hypokalemia and variable urinary pH, with alkaline urine pH if serum HCO_3^- concentration is above the tubular maximum and $\text{pH} < 5.3$ when it is below the tubular maximum. If the diagnosis of pRTA is not clear, urinary pH should be measured after an acid load with ammonium chloride (0.1 g per kilogram of body weight). In patients with pRTA, but not dRTA, urine pH decreases to < 5.3 . Because furosemide also decreases urine pH and is easier to use than ammonium chloride, measuring urine pH after the use of furosemide has been suggested in

these patients. However, this test has unacceptable rates of false-positive and -negative results. Another approach is to treat patients with HCO_3^- at 1 to 2 mEq/kg/d and check serum HCO_3^- concentration after 2 to 3 weeks. In dRTA, serum HCO_3^- concentration approaches the reference range, whereas it will remain significantly below normal in pRTA and urine will be (or become) markedly alkaline due to HCO_3^- wasting.

Treatment of pRTA

The goal is to increase serum HCO_3^- concentration as close to normal as possible. However, this is often very difficult due to the decrease in HCO_3^- tubular maximum. Oral HCO_3^- at doses of 10 to 15 mEq/kg/d with potassium supplementation is often used. Hydrochlorothiazide may be helpful by increasing the HCO_3^- tubular maximum; however, hypokalemia must be prevented with supplemental potassium and/or treated. In patients with Fanconi syndrome, phosphate supplementation is often required.

Distal RTA

dRTA reflects a failure to reabsorb HCO_3^- by intercalated cells in the collecting duct, resulting in persistent alkaline urine. It is characterized by impaired acid excretion and the inability to reduce urinary pH to < 5.3 when confronted with spontaneous acidemia or acid loading. The defect in H^+ secretion in the collecting duct leads to reduced NAE subsequent to decreased NH_4^+ , titratable acid excretion, and HCO_3^- wasting. This results in a decrease in serum HCO_3^- concentration and generation of hyperchloremic metabolic acidosis. The abnormalities in H^+ secretion in the collecting duct are secondary to defects in H^+ -ATPase, cytosolic CAII, or kidney AE1. NH_4^+ excretion is reduced in dRTA due to impaired trapping of luminal NH_3 in the collecting duct subsequent to defects in H^+ secretion. One unique feature of dRTA is very low urinary citrate levels. This is due to the increase in reabsorption of citrate by the proximal tubule in response to intracellular acidosis.

Classification of dRTA

dRTA can be hereditary (primary) or acquired (secondary).

Hereditary dRTA. The vast majority of inherited forms of dRTA are due to defects in AE1 or H^+ -ATPase. In addition, cytosolic CAII gene mutations are associated with a mixed picture of pRTA and dRTA. Mutations in the basolateral $\text{Cl}^-/\text{HCO}_3^-$ exchanger AE1 lead to the impairment of HCO_3^- absorption in A-intercalated cells in the collecting duct. Both autosomal recessive and autosomal dominant mutations have been reported. Mutations in apical H^+ -ATPase in A-intercalated cells impair H^+ secretion into the lumen of the collecting duct. Some

patients with H^+ -ATPase mutations present with sensorineural deafness. The mutations in H^+ -ATPase are predominantly of the autosomal recessive form. Mutations in CAII impair HCO_3^- reabsorption in the proximal tubule and collecting duct (mixed dRTA and pRTA). It also affects bone osteoclasts resulting in osteopetrosis.

Acquired dRTA. The most common causes are autoimmune diseases such as Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, and hypergammaglobulinemia; kidney transplantation; sickle cell disease; and drugs including ifosfamide (more commonly causing pRTA than dRTA), amphotericin B, lithium carbonate, and intravenously administered bisphosphonates such as zoledronate. In Sjögren syndrome, 3% to 6.5% of patients have complete dRTA, whereas up to 33% have incomplete dRTA. A small number have combined dRTA and pRTA, including Fanconi syndrome. A variety of antibodies against H^+ -ATPase, kidney AE1 transporter, and CAII have been reported in these patients. **Box 1** summarizes the causes of classical dRTA (type 1).

Clinical Presentation and Diagnosis

Patients with dRTA often present with signs and symptoms related to severe hypokalemia, including proximal muscle weakness, polydipsia, and polyuria. In milder cases, symptoms related to renal calculi may be the first sign of an abnormality in acid secretion. Laboratory studies show hyperchloremic metabolic acidosis with persistent urine pH > 5.3 often associated with hypokalemia. Patients with dRTA and hyperkalemic RTAs have low urinary NH_4^+ (positive urinary anion gap and low urine osmolal gap), whereas patients with hyperchloremic metabolic acidosis due to gastrointestinal HCO_3^- loss (diarrhea) usually have elevated urinary anions (negative urinary anion gap and high urine osmolal gap of more than 300–400 mEq/L). **Box 2** shows a summary of urinary NH_4^+ estimation by measuring urinary anion gap and urinary osmolal gap. **Figure 4** is a schematic depicting the differential diagnosis of hyperchloremic acidosis

Box 1. Cause of Classical Distal Renal Tubular Acidosis (Type I)

1. Primary
 - a. Familial
 - b. Sporadic
2. Secondary
 - a. Systemic diseases: Sjögren syndrome, PBS, systemic lupus erythematosus
 - b. Nephrocalcinosis: hyperparathyroidism, milk/alkali, vitamin D
 - c. Drugs: amphotericin B
 - d. Tubulointerstitial disease: Obstructive uropathy
 - e. Miscellaneous

Abbreviation: PBS, primary biliary cirrhosis.

(hyperchloremic metabolic acidosis) with respect to the source of HCO_3^- loss (gastrointestinal vs kidney) and the delineating features of serum K^+ concentration, urinary NH_4^+ excretion, and urine pH in distinguishing various types of hyperchloremic metabolic acidosis. The pathophysiology of hyperkalemic RTA (type IV) is discussed in more detail in the following sections.

Treatment of dRTA

dRTA, in contrast to pRTA, has a relatively small daily loss of HCO_3^- , often in the range of 1 to 2 mEq/kg/d. The amount of supplemental sodium or potassium bicarbonate is therefore 1 to 2 mEq/kg/d. In children, normal growth is dependent on an adequate supply of HCO_3^- and maintenance of normal serum HCO_3^- concentration. This often requires an HCO_3^- dose of 4 to 8 mEq/kg/d.

Incomplete dRTA

Incomplete dRTA is defined as having normal serum HCO_3^- concentration while lacking the ability to acidify urine when challenged with an acid-loading test. This should be considered in patients with idiopathic renal calculi with alkaline urine, as well as patients with Sjögren syndrome, children with posterior urethral valve disease, and patients with amphotericin toxicity. Kidney stones are due

Box 2. Measuring Urinary Ammonium Excretion

- Because urinary ammonia is not directly measured by the clinical laboratory, it is estimated by measuring UAG or urine osmolal gap
- Both calculations only give a qualitative and not a quantitative measure of urinary ammonia
- UAG
 - Urinary cations [$Na^+ + K^+$] – urinary anions [Cl^-]
 - In patients with hyperchloremic metabolic acidosis and normal kidneys, UAG would be < 0
 - A positive UAG indicates low urinary NH_4^+
 - UAG cannot be used if:
 - Urine pH > 7, as this would indicate the presence of bicarbonate in urine
 - Other organic anion(s) is (are) present in urine
- Urinary osmolal gap
 - Measured urinary osmolality minus (–) calculated urinary osmolality, which can be written as [(urinary $Na^+ +$ urinary K^+) \times 2 + urinary urea nitrogen/2.8 + urinary glucose/18]
 - Normal osmolal gap is usually 80–150 mEq/L
 - An elevated urine osmolal gap indicates high urine NH_4^+
 - Urinary osmolal gap cannot be used if urine contains another neutral compound such as mannitol
 - Urinary osmolal gap is not affected by the presence of other anions

Note: Estimation of urinary NH_4^+ excretion can be used as a tool to differentiate various types of hyperchloremic metabolic acidosis.

Abbreviations: NH_4^+ , ammonium ion; UAG, urinary anion gap.

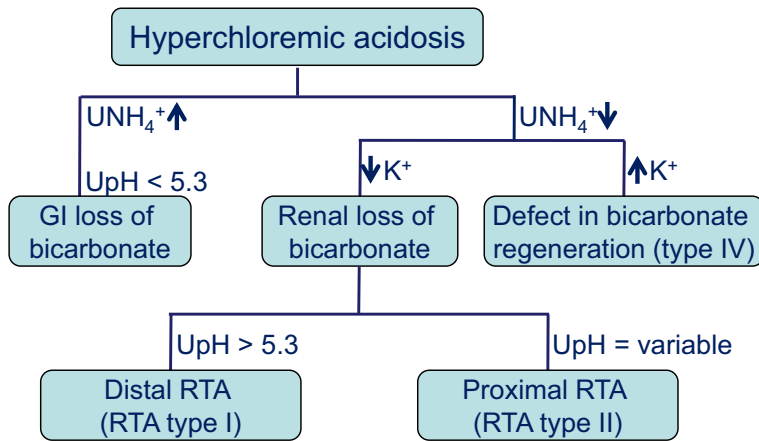


Figure 4. The differential diagnosis of hyperchloremic acidosis (hyperchloremic metabolic acidosis). The pathogenesis of renal tubular acidosis (RTA) with respect to the source of bicarbonate (HCO_3^-) loss (gastrointestinal [GI] vs kidney) and the delineating features of serum potassium ion (K^+) and urinary ammonium ion (NH_4^+) excretion (UNH_4^+) and urine pH (UpH). Caveat: Urinary NH_4^+ is variable in proximal RTA.

primarily to low urinary citrate levels combined with a high urine pH (Fig 5).

Kidney Stones and Nephrocalcinosis in RTA

Kidney stones and nephrocalcinosis are primarily seen in dRTA. The pathogenesis includes low urinary citrate, high urinary calcium, and high urinary pH favoring calcium phosphate precipitation. The use of carbonic anhydrase inhibitors (eg, acetazolamide, topiramate, and zoniramate) results in a similar scenario and is associated with an increased incidence of kidney stones. Patients with pRTA have normal urinary citrate levels and their urinary pH is commonly in an acidic range, protecting against stone formation.

Mechanism of Hypokalemia in pRTA and dRTA

Hypokalemia is a common feature of both pRTA and dRTA. The degree of hypokalemia varies and is often more severe in patients with dRTA. In hereditary dRTA, hypokalemia is a cardinal clinical feature, independent of the genetic mutation, although it is more severe in autosomal recessive forms due to a mutation in subunits of the H^+ -ATPase pump. The mechanism of hypokalemia is only partially

understood and involves an increase in aldosterone levels due to sodium wasting, as well as metabolic acidosis. In amphotericin B-induced dRTA, both the impairment in H^+ secretion and K^+ loss are due to a defect in membrane permeability. However, this defect is unique to amphotericin B toxicity and has not been shown in other forms of dRTA. In pRTA, treatment with HCO_3^- supplement will result in marked bicarbonaturia. An increase in urinary HCO_3^- excretion may obligate an increase in K^+ secretion, thereby worsening the hypokalemia. Please refer to Fig 4 for a summary of features of various types of hyperchloremic metabolic acidosis with regard to serum K^+ level, urine pH, and urine NH_4^+ excretion.

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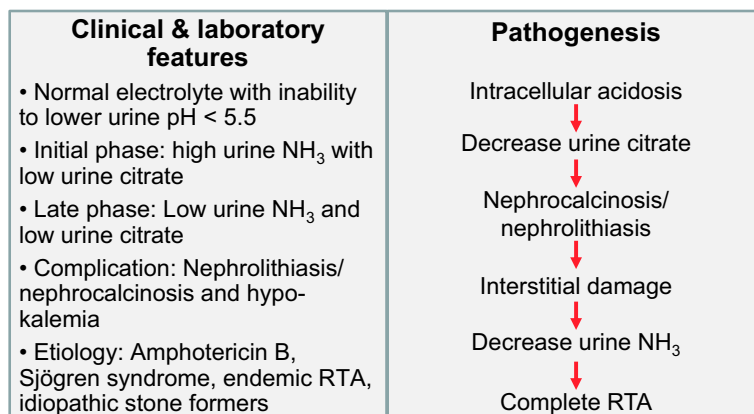


Figure 5. Clinical and laboratory features, pathogenesis, and major complications of incomplete distal renal tubular acidosis (idRTA). Abbreviation: NH_3 , ammonia.

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Hyperkalemic RTA

Hyperkalemic RTA (type IV) is due to a defect in regeneration of HCO_3^- secondary to lack of adequate urinary NH_4^+ . The most common cause of low urinary NH_4^+ in hyperkalemic RTA is hypoaldosteronism in conjunction with hyperkalemia. Hypoaldosteronism should be considered in all patients with persistent hyperkalemia for whom there is no obvious cause (eg, kidney failure, use of potassium supplements, or potassium-sparing diuretics). A hypoaldosterone state could be due to hyporeninism seen in patients with kidney disease or from a defect in the renin-angiotensin-aldosterone pathway. In hyperkalemic RTA with normal or high aldosterone levels, the defect is in response to aldosterone; for example, patients on ENaC blockers. Hyperkalemia can impair NH_4^+ excretion by 2 major mechanisms: intracellular alkalosis due to the entry of K^+ into proximal tubule cells in exchange for Na^+ and H^+ , inhibiting ammoniogenesis, or a decrease in medullary NH_4^+ absorption through inhibition of its reabsorption in the thick ascending limb of loop of Henle by the $Na^+/K^+/2Cl^-$ cotransporter, where K^+ and NH_4^+ compete for the same site on this transporter.

Classification of Hyperkalemic RTA

Hyperkalemic RTA can be inherited or acquired.

Hereditary hyperkalemic RTA. Inherited hypoaldosteronism is due to a decrease in aldosterone synthesis, such as in congenital isolated hypoaldosteronism or pseudohypoaldosteronism type 2 (Gordon syndrome), due to an increase in sodium chloride absorption in the distal convoluted tubule resulting in secondary hypoaldosteronism. It could also be due to resistance to aldosterone action as seen in type 1 pseudohypoaldosteronism.

Acquired hyperkalemic RTA. Acquired hypoaldosteronism may be secondary to hyporeninism, which is most commonly seen in patients with mild to moderate chronic kidney disease due to diabetic nephropathy or chronic interstitial nephritis. Primary adrenal insufficiency can result from autoimmune adrenalitis, infectious adrenalitis (eg, HIV), and other disorders. Hypoaldosteronism may also present in severely ill patients due to unknown mechanisms. Obstructive uropathy may present with hyperkalemic RTA due to impaired H^+ and K^+ secretion in the collecting duct. Urinary pH in these patients may be >5.5 despite the presence of acidemia. Drugs are a major cause of acquired hyperkalemic RTA (Fig 6). The major drugs and mechanisms resulting in acquired hyperkalemic RTA are summarized as follows:

- Potassium-sparing diuretics: these drugs cause hyperkalemic RTA by either blocking the action of aldosterone on the collecting tubule cells through competing for the aldosterone receptor (spironolactone or eplerenone) or inhibiting the ENaC (amiloride)
- Antibiotics: 2 antibiotics, trimethoprim and pentamidine, can cause hyperkalemia by inhibiting ENaC
- Nonsteroidal anti-inflammatory drugs: nonsteroidal anti-inflammatory drugs interfere with the secretion of renin and also impair angiotensin II-induced release of aldosterone
- Calcineurin inhibitors: both cyclosporine and tacrolimus can cause hyperkalemia by inducing aldosterone resistance. The effect of tacrolimus is through activation of the thiazide-sensitive Na^+/Cl^- cotransporter and inhibition of the renal outer medullary K^+ channel (ROMK) in the distal nephron
- Angiotensin inhibitors: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers,

and renin inhibitors can cause hyperkalemia by reducing aldosterone synthesis

- Heparin and low-molecular-weight heparin: can cause hyperkalemia by inhibiting adrenal gland release of aldosterone from the zona glomerulosa

Diagnosis of Hyperkalemic RTA

Diagnosis of hyperkalemic RTA is usually straightforward and based on the initial clinical and laboratory presentation. However, in patients with more complex cases, further studies are done to document low NH_4^+ and K^+ excretion. This includes estimating urinary NH_4^+ excretion by measuring urinary anion and/or urinary osmolal gaps (Box 2). Urine pH should be appropriately acidic ($\text{pH} < 5.5$), although $\text{pH} > 5.5$ is seen in obstructive uropathy. Low urinary K^+ excretion can be assessed by a transtubular K^+ gradient or urinary potassium-creatinine ratio. To establish the cause of hyperkalemic RTA, specific causes including drugs should be sought. When indicated, random serum renin and

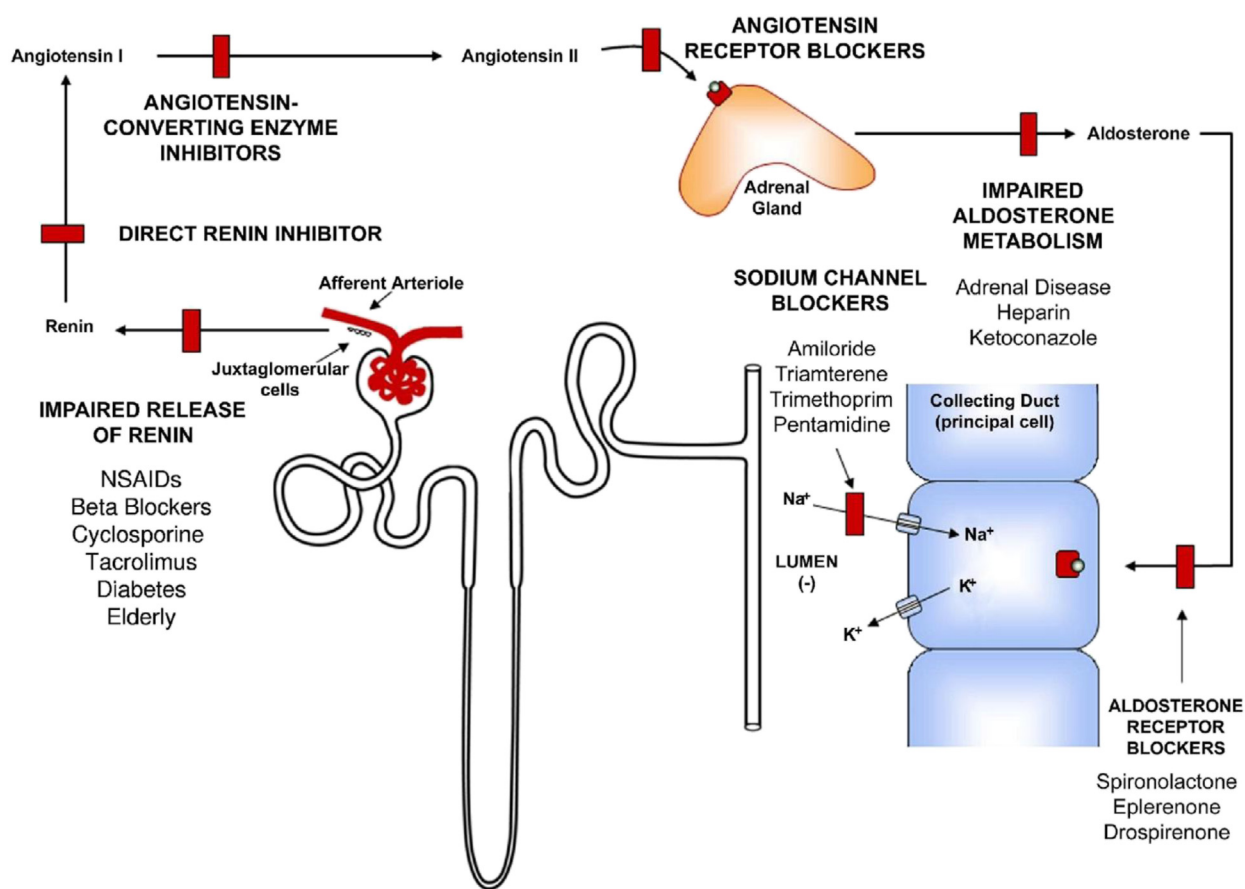


Figure 6. Pathogenesis of hyperkalemia. Medications, diseases, and the renin-angiotensin II-aldosterone axis and their role in potassium ion (K^+) homeostasis. Abbreviations: Na^+ , sodium ion; NSAID, nonsteroidal anti-inflammatory drug. Reproduced from Palmer ("A Physiologic-Based Approach to the Evaluation of a Patient With Hyperkalemia" *AJKD* 2010;56:387-393) with permission of the National Kidney Foundation.

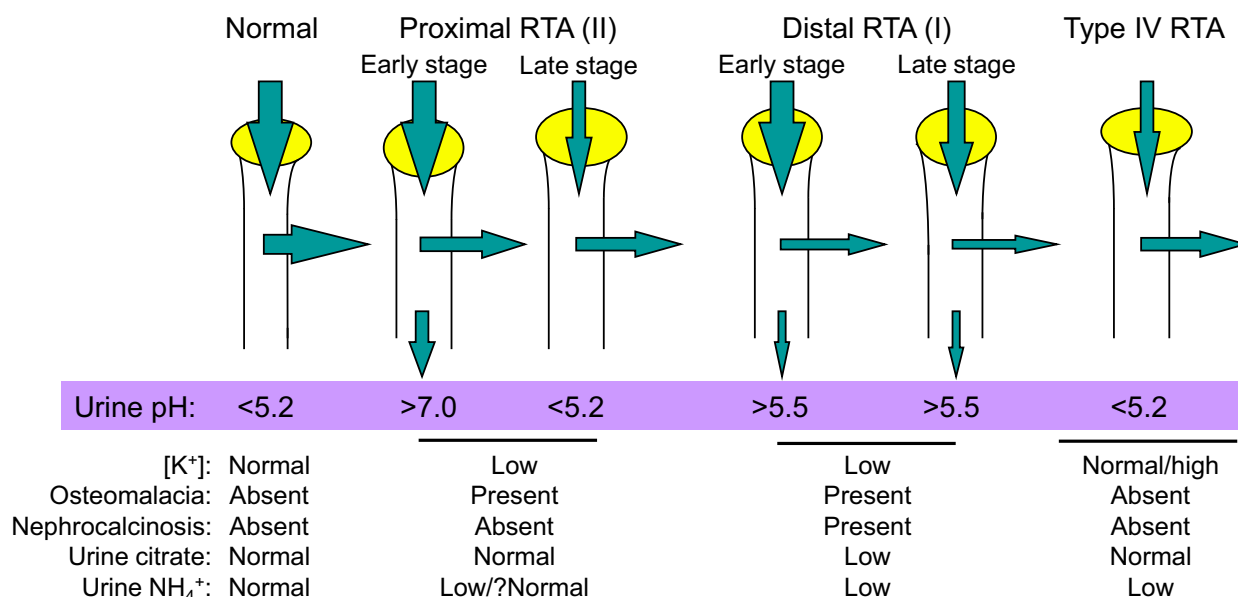


Figure 7. Pathogenesis, classification, and clinical presentation of renal tubular acidosis (RTA). The pathogenesis and contrasting features of proximal RTA (type II), distal RTA (type I), and hyperkalemic RTA (type IV) are depicted.

aldosterone levels are helpful in establishing the diagnosis of hypoaldosteronism, with or without hyporeninism. Urinary obstruction should always be considered when other more common causes have been ruled out. Figure 7 summarizes the distinctive features of pRTA (type II), dRTA (type I), and hyperkalemic RTA (type IV) with respect to their pathogenesis and emphasis on the contrasting presence of nephrocalcinosis and generation of kidney stones, urine citrate, and NH₄⁺ excretion.

Treatment of Hyperkalemic RTA

The goal of the treatment initially is to normalize serum K⁺ concentration because this may improve metabolic acidosis by increasing urinary NH₃ responsible for buffering secreted H⁺, as well as by enhancing HCO₃⁻ generation in the proximal tubule by enhanced glutamine metabolism (Fig 3). If this is inadequate, attempts should be made to improve metabolic acidosis. Box 3 discusses long-term treatment of hyperkalemia in patients with hyperkalemic RTA.

Additional Readings

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Box 3. Long-term Treatment of Hyperkalemia in Patients With Hyperkalemic Renal Tubular Acidosis

1. Discontinue all drugs affecting potassium
2. Restrict dietary potassium
3. Control hyperglycemia
4. Treat metabolic acidosis
5. Treat volume depletion
6. Use loop diuretics
7. Mineralocorticoids
8. Kayexalate

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