



# Renal Tubular Acidosis and Management Strategies: A Narrative Review

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## ABSTRACT

Renal tubular acidosis (RTA) occurs when the kidneys are unable to maintain normal acid–base homeostasis because of tubular defects in acid excretion or bicarbonate ion reabsorption. Using illustrative clinical cases, this review describes the main types of RTA observed in clinical practice and provides an overview of their diagnosis and treatment. The three major forms of RTA are distal RTA (type 1; characterized by impaired acid excretion),

proximal RTA (type 2; caused by defects in reabsorption of filtered bicarbonate), and hyperkalemic RTA (type 4; caused by abnormal excretion of acid and potassium in the collecting duct). Type 3 RTA is a rare form of the disease with features of both distal and proximal RTA. Accurate diagnosis of RTA plays an important role in optimal patient management. The diagnosis of distal versus proximal RTA involves assessment of urinary acid and bicarbonate secretion, while in hyperkalemic RTA, selective aldosterone deficiency or resistance to its effects is confirmed after exclusion of other causes of hyperkalemia. Treatment options include alkali therapy in patients with distal or proximal RTA and lowering of serum potassium concentrations through dietary modification and potential new pharmacotherapies in patients with hyperkalemic RTA including newer potassium binders.

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### Key Summary Points

Normal acid–base homeostasis is maintained by the kidneys and respiratory system

Renal tubular acidosis (RTA) occurs when the kidneys are unable to adequately reclaim filtered bicarbonate or excrete sufficient hydrogen ions because of defects in tubular transport

Three main types of RTA are common in clinical practice: distal (type 1), proximal (type 2), and hyperkalemic (type 4) RTA

Differential diagnosis of RTA should consider presenting signs and symptoms, the anion gap, serum biochemistry, and urine pH

Treatment options depend on the type of RTA diagnosed; alkali therapy may be used in patients with type 1 or 2 RTA, and newer potassium binders may be beneficial for patients with type 4 RTA

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13286027>.

## INTRODUCTION

The maintenance of acid–base homeostasis is a major function of the body, accomplished by intracellular and extracellular buffering mechanisms, exhalation of carbon dioxide (CO<sub>2</sub>)

through the respiratory system, and acid excretion by the kidneys [1]. In healthy individuals ingesting a typical Western diet, metabolism produces acid or alkali components [1], with a daily net acid production of approximately 1 mmol/kg of body weight per day [2]. The amino acids lysine and arginine are metabolized to generate acids, while metabolism of glutamate and aspartate and organic anions, such as acetate and citrate, yield alkali [3]. Metabolism of sulfur-containing amino acids (i.e., methionine and cysteine) yields sulfuric acid, while dietary phosphate yields phosphoric acid [3].

Metabolic acidosis is defined as an excess in non-volatile acid load that results in a primary decrease in plasma bicarbonate (HCO<sub>3</sub><sup>-</sup>) associated with a low plasma pH [1]. Metabolic acidosis can have a normal or high anion gap, where the anion gap refers to difference between the number of cations (i.e., sodium [Na<sup>+</sup>] and potassium [K<sup>+</sup>]) and the number of anions (i.e., chloride [Cl<sup>-</sup>] and HCO<sub>3</sub><sup>-</sup>) [4]. Typically, an anion gap greater than 20 mmol/L may be considered as high; anion gaps greater than 18 mmol/L should be further investigated [4].

Renal tubular acidosis (RTA) develops as a consequence of impaired urinary acidification and is characterized by normal anion gap metabolic acidosis. RTA occurs when the kidneys are unable to adequately reclaim filtered HCO<sub>3</sub><sup>-</sup> or secrete sufficient hydrogen ions (H<sup>+</sup>) to maintain acid–base homeostasis [5]. This review describes the physiological processes involved in the maintenance of normal acid–base homeostasis and provides an overview of the different types of RTA. The clinical presentation, differential diagnosis, and management options for patients with RTA are also discussed.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## NORMAL ACID–BASE HOMEOSTASIS

### Kidneys

The kidneys contribute to the maintenance of acid–base homeostasis by reabsorbing  $\text{HCO}_3^-$  in the proximal tubule, as well as regenerating  $\text{HCO}_3^-$  in the cortical collecting duct [1, 5].  $\text{HCO}_3^-$  reabsorption involves secretion of  $\text{H}^+$  into the proximal tubule through the  $\text{Na}^+/\text{H}^+$  exchanger 3 (NHE3) and  $\text{H}^+$ -adenosine triphosphatase ( $\text{H}^+$ -ATPase) transporters, after which luminal  $\text{HCO}_3^-$  reacts with secreted  $\text{H}^+$  to form  $\text{CO}_2$  and water, a process that is catalyzed by membrane-bound carbonic anhydrase isoform IV (Fig. 1a) [1, 5, 6].  $\text{CO}_2$  is then freely absorbed across the proximal tubular membrane, where cytosolic carbonic anhydrase II catalyzes its reaction with water to form carbonic acid that rapidly breaks down to  $\text{HCO}_3^-$ , which is reabsorbed into the blood through the  $\text{Na}^+/\text{HCO}_3^-$  cotransporter (NBCe1), and  $\text{H}^+$ , which is then secreted back into the tubular lumen [5].  $\text{HCO}_3^-$  is also reabsorbed by a similar mechanism in the thick ascending limb of the loop of Henle (Fig. 1b) [6].

In the collecting duct,  $\alpha$ -intercalated cells secrete  $\text{H}^+$  by an apical  $\text{H}^+$ -ATPase. This process generates  $\text{HCO}_3^-$ , which is transported into the blood by the basolateral  $\text{Cl}^-/\text{HCO}_3^-$  exchanger kidney anion exchanger 1 (AE1).  $\beta$ -Intercalated cells secrete  $\text{HCO}_3^-$  into the lumen of the cortical collecting duct in exchange for  $\text{Cl}^-$  through the apical  $\text{Cl}^-/\text{HCO}_3^-$  exchanger pendrin [5].  $\text{HCO}_3^-$  secretion is driven by  $\text{H}^+$  secretion across the basolateral surface of the cell via an  $\text{H}^+$ -ATPase (Fig. 1c, d) [6].

In the cortical collecting duct,  $\text{H}^+$  secretion by apical  $\text{H}^+$ -ATPase in  $\alpha$ -intercalated cells is regulated by apical epithelial  $\text{Na}^+$  channels (ENaC) in principal cells, as well as aldosterone, angiotensin II, and the calcium-sensing receptor [5]. Specifically, reabsorption of  $\text{Na}^+$  through ENaC creates a lumen-negative charge secondarily increasing the rate of  $\text{H}^+$  secretion. Secreted  $\text{H}^+$  is buffered by ammonia ( $\text{NH}_3$ ) and

titratable acids, such as phosphate.  $\text{NH}_3$  is produced as the result of glutamine metabolism and secreted into the proximal tubule lumen, where it combines with  $\text{H}^+$  to form ammonium ( $\text{NH}_4^+$ ; Fig. 2a) [1, 5, 6]. Following reabsorption of  $\text{NH}_4^+$  in the medullary thick ascending limb by substituting  $\text{K}^+$  for  $\text{NH}_4^+$  on apical  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  cotransporters (Fig. 2b),  $\text{NH}_3$  is secreted into the collecting duct, whereupon it combines with  $\text{H}^+$  secreted from  $\alpha$ -intercalated cells to form excreted  $\text{NH}_4^+$  [1, 5].

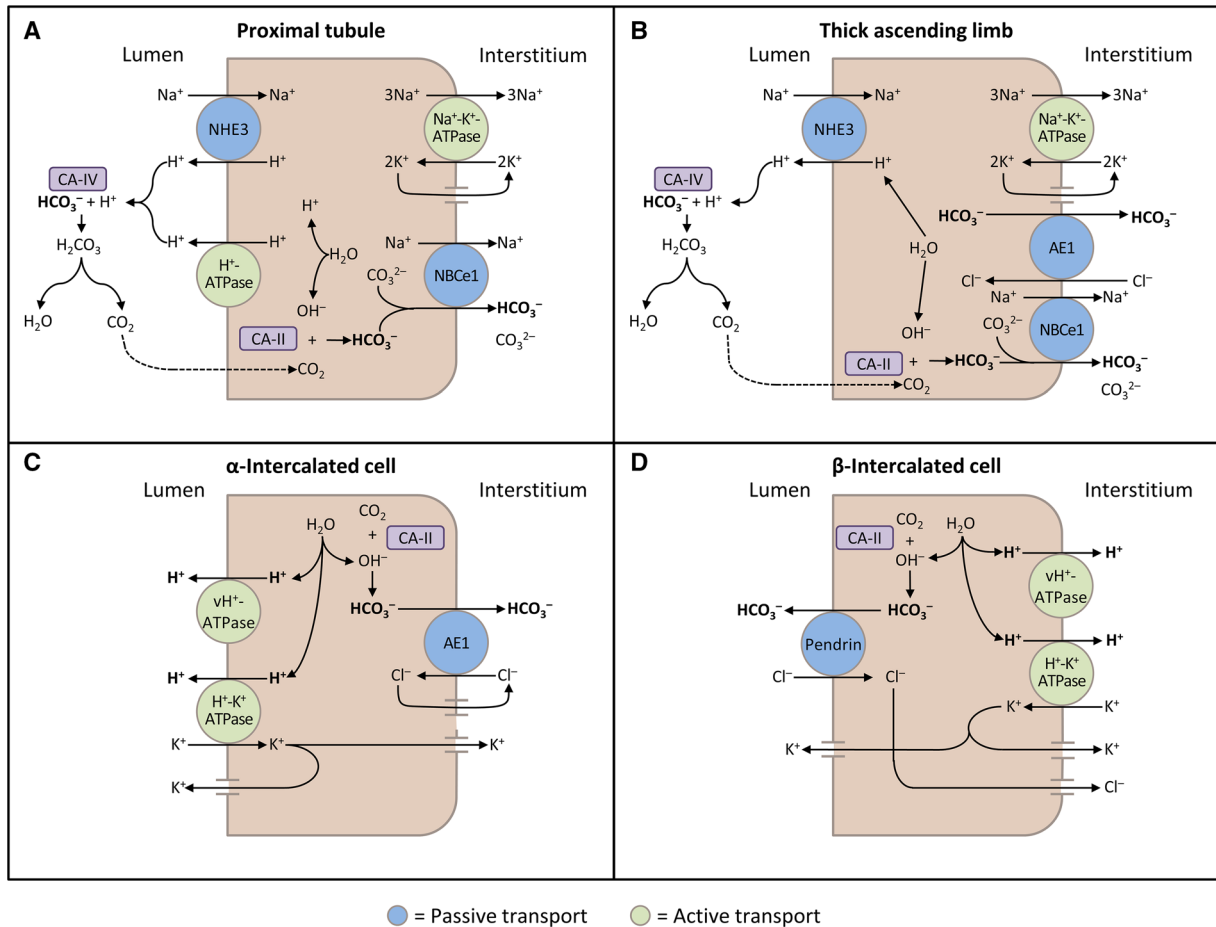
### Respiratory System

Acid–base homeostasis is also maintained by the brainstem and lungs. Alveolar ventilation increases in response to a decrease in cerebral interstitial pH (or vice versa) [1]. A small decrease in plasma pH stimulates alveolar ventilation and lowers arterial partial pressure of  $\text{CO}_2$  ( $\text{pCO}_2$ ) under normal conditions, which minimizes the drop in plasma pH [1].

## CLASSIFICATION OF RTA

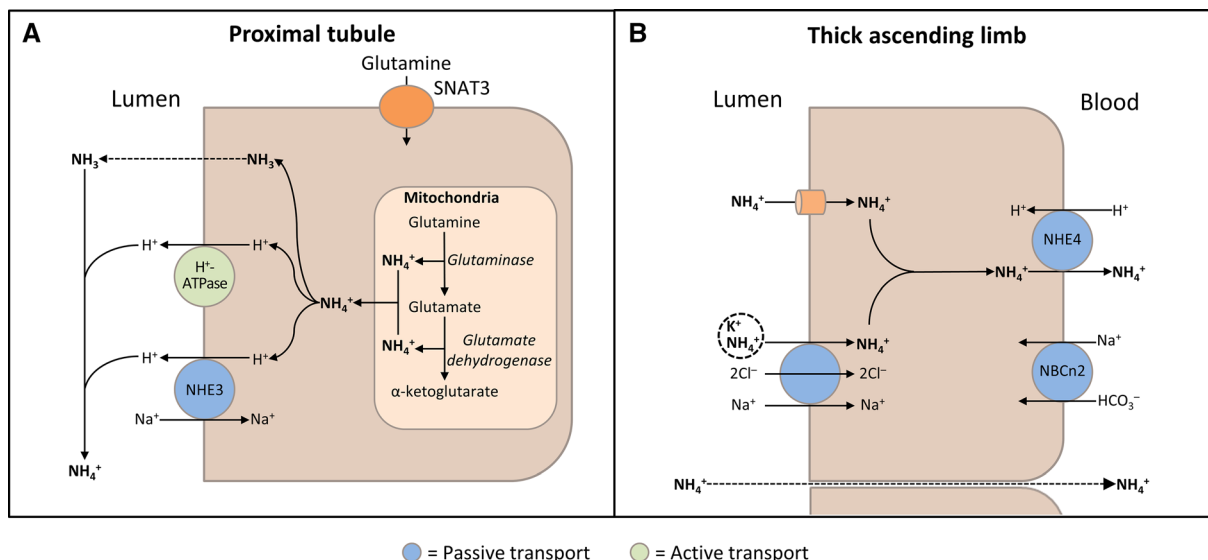
RTA can occur as the result of one or more defects in tubular transport of  $\text{H}^+$  or  $\text{HCO}_3^-$  [7]. It can occur in patients with a normal or only mildly decreased glomerular filtration rate (GFR), as well as those with chronic kidney disease (CKD) [7, 8]. RTA is a cause of hyperchloremic normal anion gap acidosis, in which the loss of serum  $\text{HCO}_3^-$  leads to retention of  $\text{Cl}^-$  so that the anion gap remains normal [9].

Three types of RTA are commonly observed in clinical practice (Fig. 3; Table 1). Types 1 and 2 RTA are caused by defects in the distal and proximal tubule, respectively, and type 4 RTA is characterized by abnormal excretion of acid and  $\text{K}^+$  in the collecting duct, which leads to hyperkalemic acidosis. Type 3 RTA is rare and has features of both distal and proximal RTA (because of the rarity of this condition, it will not be discussed further) [5]. Here, we use illustrative cases to describe the clinical characteristics of the three main forms of RTA.



**Fig. 1** Schematic diagrams illustrating bicarbonate ( $\text{HCO}_3^-$ ) reabsorption and regeneration in the kidney. **a**  $\text{HCO}_3^-$  reabsorption in the proximal tubule. Hydrogen ions ( $\text{H}^+$ ) are secreted into the lumen via apical sodium ( $\text{Na}^+$ )/ $\text{H}^+$  exchanger 3 (NHE3) and  $\text{H}^+\text{-ATPase}$  transporters. Apical carbonic anhydrase (CA) IV catalyzes the reaction between  $\text{H}^+$  and  $\text{HCO}_3^-$ , which forms  $\text{H}_2\text{CO}_3$  that rapidly dissociates to water and carbon dioxide ( $\text{CO}_2$ ).  $\text{CO}_2$  diffuses back across the apical membrane, where CA-II catalyzes its reaction with intracellular hydroxide ions ( $\text{OH}^-$ ) to form  $\text{H}^+$  and  $\text{HCO}_3^-$ .  $\text{HCO}_3^-$  is transported across the basolateral membrane by the  $\text{Na}^+/\text{HCO}_3^-/\text{CO}_3^{2-}$  cotransporter (NBCe1). **b**  $\text{HCO}_3^-$  reabsorption in the thick ascending limb. As in the proximal tubule,  $\text{H}^+$  is secreted into the lumen via NHE3, where it reacts with  $\text{HCO}_3^-$  to release  $\text{CO}_2$  that diffuses back across the apical membrane.  $\text{HCO}_3^-$  is transported across the basolateral membrane by NBCe1 and the kidney anion exchanger (AE1). **c**  $\text{H}^+$  secretion by  $\alpha$ -intercalated

cells in cortical collecting duct (CCD).  $\text{H}^+$  is secreted into the lumen by  $\text{H}^+/\text{K}^+\text{-ATPase}$  and vacuolar (v)  $\text{H}^+\text{-ATPase}$  transporters on the apical membrane. Intracellular  $\text{OH}^-$  generated by  $\text{H}^+$  secretion reacts with  $\text{CO}_2$  via CA-II to form  $\text{HCO}_3^-$ , which is removed by basolateral AE1. The resulting intracellular chloride ( $\text{Cl}^-$ ) exits via conductance channels in the basolateral membrane. Luminal  $\text{K}^+$  transported into the cell via  $\text{H}^+/\text{K}^+\text{-ATPase}$  can exit via channels in the apical or basolateral membrane, depending on  $\text{K}^+$  balance. **d**  $\text{HCO}_3^-$  secretion by  $\beta$ -intercalated cells in CCD.  $\text{H}^+\text{-ATPase}$  transports  $\text{H}^+$  across the basolateral membrane. Intracellular  $\text{OH}^-$  generated by  $\text{H}^+$  secretion reacts with  $\text{CO}_2$  via CA-II to form  $\text{HCO}_3^-$ , which is transported into the lumen by the apical  $\text{Cl}^-/\text{HCO}_3^-$  exchanger pendrin. Intracellular  $\text{Cl}^-$  exits via conductance channels in the basolateral membrane (These figures were published in *Comprehensive Clinical Nephrology: 5th Edition*, Palmer BF, Normal acid–base balance, pp. 142–148, Copyright Elsevier (2014) [6])



**Fig. 2** Schematic diagrams illustrating ammonia ( $\text{NH}_3$ ) production and transport in the kidney. **a**  $\text{NH}_3$  production in the proximal tubular cells. After glutamine uptake via sodium ( $\text{Na}^+$ )-coupled neutral amino acid transporter 3 (SNAT3), mitochondrial glutamine metabolism results in production of ammonium ( $\text{NH}_4^+$ ).  $\text{NH}_3$  passively diffuses across apical membrane and hydrogen ( $\text{H}^+$ ) is transported via apical  $\text{Na}^+/\text{H}^+$  exchanger 3 (NHE3) and  $\text{H}^+$ -ATPase;  $\text{NH}_3$  and  $\text{H}^+$  combine in the lumen to form  $\text{NH}_4^+$ . **b**  $\text{NH}_3$  transport in the thick ascending limb. Lumen-

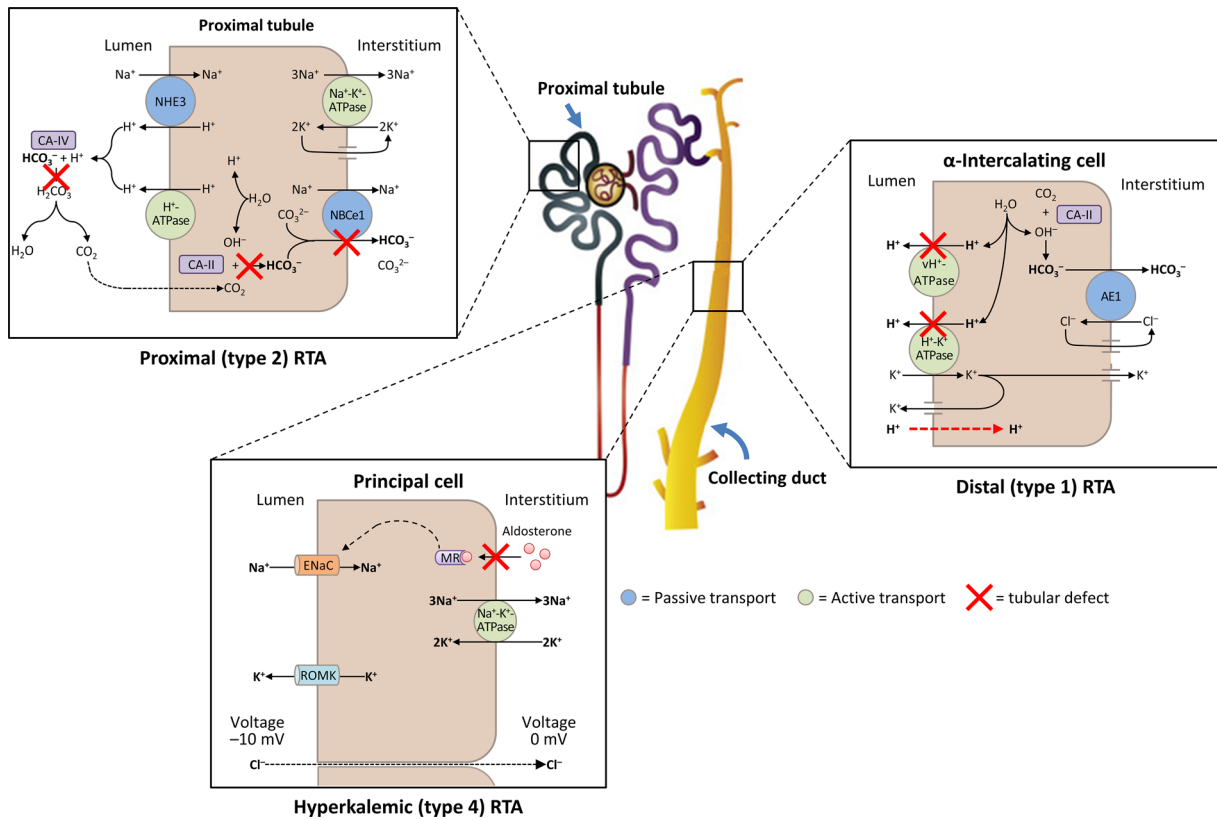
positive voltage drives passive paracellular transport of  $\text{NH}_4^+$  from the lumen into the blood. By substituting for potassium ( $\text{K}^+$ ),  $\text{NH}_4^+$  is also transported into the cell via the  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  transporter and the apical membrane  $\text{K}^+$  channel (ROMK). The basolateral  $\text{Na}^+/\text{bicarbonate}$  ( $\text{HCO}_3^-$ ) cotransporter (NBCn2) may play a role in maintaining cellular pH.  $\text{NH}_4^+$  crosses the basolateral membrane into the blood via NHE4 (Adapted with permission from Palmer 2014 [6])

### Distal RTA (Type 1)

#### Clinical Case Presentation 1

A 34-year-old woman presents with diffuse muscle weakness over several days. She also reports dry eyes and dry mouth over the last several months. Laboratory analysis shows the following:  $\text{Na}^+$  141 mmol/L,  $\text{K}^+$  2.5 mmol/L,  $\text{Cl}^-$  112 mmol/L, and  $\text{HCO}_3^-$  16 mmol/L, and an arterial blood gas test shows pH 7.32 and  $\text{pCO}_2$  31 mmHg. Serum creatinine is 1.4 mg/dL and urine pH is 6.8. Ultrasound imaging shows normal sized kidneys with evidence of numerous calcifications distributed throughout both kidneys. The patient is diagnosed with type 1 RTA, thought to be secondary to underlying Sjögren’s syndrome.

Patients with distal (type 1) RTA are unable to acidify their urine despite severe metabolic acidosis. Distal RTA is characterized by impaired urinary acid secretion and evidence of kidney  $\text{K}^+$  wasting with either normal or minimally reduced GFR and persistently alkaline urine pH (> 5.3; Table 1) [10]. Patients with distal RTA often present with symptoms relating to hypokalemia, such as polydipsia and polyuria due to impaired urinary concentration ability, as well as muscle weakness, as seen in Clinical Case Presentation 1. This patient also presented with nephrolithiasis; distal RTA is a risk factor for nephrolithiasis and nephrocalcinosis due to hypercalciuria and hypocitraturia, combined with a persistently alkaline urine pH [5, 11]. Children with distal RTA also commonly



**Fig. 3** A schematic diagram illustrating the underlying kidney tubule defects causing the different types of renal tubular acidosis (RTA). Distal (type 1) RTA is caused by either impaired hydrogen ( $\text{H}^+$ ) secretion by vacuolar (v)  $\text{H}^+$ -ATPase or  $\text{H}^+$ / $\text{K}^+$ -ATPase or increased  $\text{H}^+$  permeability of luminal membrane by  $\alpha$ -intercalated cells of the collecting duct, which leads to a reduction in net  $\text{H}^+$  secretion. Proximal (type 2) RTA is caused by defects in bicarbonate ( $\text{HCO}_3^-$ ) reabsorption in the proximal tubule, due to either impaired  $\text{HCO}_3^-$  transport across the

basolateral membrane or inhibition of carbonic anhydrase (CA) activity. Hyperkalemic (type 4) RTA is caused by aldosterone deficiency or resistance, which leads to reduced  $\text{Na}^+$  (sodium) reabsorption by principal cells of the collecting duct and decreased transepithelial voltage, leading to diminished  $\text{H}^+$  secretion by  $\alpha$ -intercalated cells and  $\text{K}^+$  secretion by principal cells. AE1 kidney anion exchanger, ENaC epithelial  $\text{Na}^+$  channel, MR mineralocorticoid receptor, NHE3  $\text{Na}^+$ / $\text{H}^+$  exchanger 3, ROMK apical membrane  $\text{K}^+$  channel

present with failure to thrive, growth retardation, and rickets [11, 12].

Distal RTA is caused by impaired distal acidification of the urine due to a reduction in net  $\text{H}^+$  secretion in the distal nephron, which results in impaired  $\text{HCO}_3^-$  regeneration. This defect may be due to impaired  $\text{H}^+$  secretion through decreased net activity of  $\text{H}^+$ -ATPase or  $\text{H}^+$ / $\text{K}^+$ -ATPase (i.e., secretory defect) or increased  $\text{H}^+$  permeability of the luminal membrane (i.e., gradient defect) [10, 13]. Patients with distal RTA typically develop

hyperchloremic, hypokalemic metabolic acidosis with a normal anion gap [11, 14]. In general, most patients develop hypokalemia as decreased distal secretion of  $\text{H}^+$  via  $\text{H}^+$ -ATPase or  $\text{H}^+$ / $\text{K}^+$ -ATPase ultimately causes decreased  $\text{K}^+$  reabsorption (i.e., renal  $\text{K}^+$  wasting) [13, 15]. If  $\text{H}^+$ / $\text{K}^+$ -ATPase is primarily affected, then less  $\text{K}^+$  will be reabsorbed. A likely greater mechanism underlying renal  $\text{K}^+$  wasting is the effect of systemic acidosis on proximal tubular function due to defects in vacuolar  $\text{H}^+$ -ATPase. Acidemia reduces net proximal fluid reabsorption, which

**Table 1** Summary of renal tubular acidosis classification, diagnostic characteristics, and treatment options

	<b>Distal (type 1) RTA</b>	<b>Proximal (type 2) RTA</b>	<b>Hyperkalemic (type 4) RTA</b>
Primary defect	Decreased distal acid excretion or increased H <sup>+</sup> membrane permeability	Decreased proximal reabsorption of HCO <sub>3</sub> <sup>-</sup>	Reduced excretion of acid and K <sup>+</sup> in the collecting duct
Symptoms	Polydipsia, polyuria, muscle weakness, nephrolithiasis, nephrocalcinosis, growth retardation or failure to thrive, rickets	Muscle weakness or paralysis (if severely hypokalemic), growth retardation in early childhood	Often asymptomatic, occasional muscle weakness of cardiac arrhythmia
Urine pH	> 5.3	< 5.5	< 5.5
Serum HCO <sub>3</sub> <sup>-</sup>	10–20 mmol/L	16–20 mmol/L	16–22 mmol/L
Serum K <sup>+</sup>	Low (< 3.5 mmol/L)	Low (< 3.5 mmol/L)	High (5.5–6.5 mmol/L)
Serum anion gap	Normal	Normal	Normal
Diagnostic tests	Positive urinary anion gap after NH <sub>4</sub> <sup>+</sup> loading test	Fractional excretion of HCO <sub>3</sub> <sup>-</sup> > 15% or urine pH > 7.5 after HCO <sub>3</sub> <sup>-</sup> loading test  Glycosuria, hypophosphatemia, and hypouricemia indicates Fanconi syndrome	Urinary K <sup>+</sup> < 40 mmol/L or fractional K <sup>+</sup> excretion < 20%, abnormal serum aldosterone, with near-normal renal function
Treatment			
Diet and lifestyle modifications	Increased citrus fruit and fluid intake, restricted intake of Na <sup>+</sup> , oxalate, fructose, and animal protein, normal Ca <sup>2+</sup> intake	Limit acid-based foods (animal source protein), increase alkali-based foods (fruits and vegetables)	Dietary K <sup>+</sup> restriction, increase alkali-based foods, limit acid-based foods
Pharmacotherapy	NaHCO <sub>3</sub> or KHCO <sub>3</sub> (1–2 mmol/kg/day), KCl or K-citrate (in patients with severe hypokalemia)	Alkali therapy (usually K-citrate 10–15 mmol/kg/day), fluids, electrolytes, vitamin D, phosphate, hydrochlorothiazide	Low-dose fludrocortisone, loop diuretics (if fludrocortisone not tolerated), oral NaHCO <sub>3</sub> if serum HCO <sub>3</sub> <sup>-</sup> < 22 mmol/L, K <sup>+</sup> binders (patiromer or SZC)

Ca<sup>2+</sup> calcium ion, HCO<sub>3</sub><sup>-</sup> bicarbonate, K<sup>+</sup> potassium, KCl potassium chloride, Na<sup>+</sup> sodium, NaHCO<sub>3</sub> sodium bicarbonate, NH<sub>4</sub><sup>+</sup> ammonium, RTA renal tubular acidosis, SZC sodium zirconium cyclosilicate

leads to volume contraction and activation of the renin–angiotensin–aldosterone system (RAAS), resulting in decreased proximal tubular  $\text{Na}^+$  reabsorption and increased distal delivery of  $\text{Na}^+$  to the cortical collecting duct. These processes, along with increased aldosterone secretion, lead to increased  $\text{K}^+$  secretion [13].

Impaired  $\text{Na}^+$  reabsorption in the cortical collecting duct due to loss of  $\text{H}^+$ -ATPase function also leads to increased  $\text{Na}^+$  delivery and urine flow to the medullary collecting duct [10]. Increased distal  $\text{Na}^+$  delivery stimulates expression of ENaC to promote  $\text{Na}^+$  reabsorption, and the resultant increase in ENaC-dependent  $\text{Na}^+$  reabsorption stimulates  $\text{K}^+$  channel-dependent  $\text{K}^+$  secretion [10]. Increased urinary flow activates large conductance big  $\text{K}^+$  channels, which further promote  $\text{K}^+$  secretion and contribute to hypokalemia development [16]. In contrast, renal  $\text{Na}^+$  wasting is suspected to be caused by natriuresis due to increased levels of brain natriuretic peptide or reduced sympathetic tone in the kidneys [17].

On the basis of the underlying defect, distal RTA may be classified as hereditary (primary) or acquired (secondary) [5]. For example, primary distal RTA may be caused by autosomal recessive mutations in A4 (*ATP6VOA4*) and B1 (*ATP6B1*) subunit genes of vacuolar  $\text{H}^+$ -ATPase [18–20]. Mutations in the *AE1* gene encoding the basolateral  $\text{Cl}^-/\text{HCO}_3^-$  exchanger protein of  $\alpha$ -intercalated cells are associated with autosomal dominant primary distal RTA [21]. Acquired distal RTA may occur as a result of some medications, including amphotericin B [22], lithium [23], and high doses of ibuprofen [24]. Secondary distal RTA often develops in association with systemic diseases [7], such as Sjögren's syndrome (as in Clinical Case Presentation 1) [25, 26], systemic lupus erythematosus [27], or primary sclerosing cholangitis [28], and inherited conditions, such as sickle cell anemia [29] and Wilson's disease [30].

$\text{NH}_3$  synthesis is normally increased in response to low pH and low serum  $\text{K}^+$  concentrations [5, 7]; however, the inability to acidify

luminal fluid in distal RTA causes decreased  $\text{NH}_3$  secretion in the proximal tubule [7], which may lead to the development of elevated serum  $\text{NH}_3$  concentrations (hyperammonemia) in some cases [11, 31]. Furthermore, medullary transfer of  $\text{NH}_4^+$  may be impaired because of renal interstitial disease, which often occurs in association with the patient's underlying condition or as a result of hypokalemia (i.e., kaliopenic nephropathy) or nephrocalcinosis [7].

Distal RTA is often associated with recurrent nephrolithiasis, nephrocalcinosis, and bone disease [32].  $\text{H}^+$  retention also leads to decreases in renal calcium reabsorption and increases in calcium release from bones, which causes hypercalciuria [32]. Citrate reabsorption in the proximal tubules is elevated in distal RTA as a result of increased  $\text{Na}^+$ -dependent dicarboxylate transporter 1 activity, and this leads to hypocitraturia [11, 32]. Hypercalciuria, hypocitraturia, and alkaline urinary pH all promote calcium phosphate precipitation [11, 32].

Incomplete distal RTA has many clinical characteristics in common with distal RTA, including hypocitraturia and alkaline urine pH, and may also be associated with nephrolithiasis and nephrocalcinosis [32]. However, in contrast to overt distal RTA, patients with incomplete distal RTA often have normal serum  $\text{HCO}_3^-$  concentrations and  $\text{NH}_3$  secretion is typically normal or occasionally increased [5, 32].

Clinical Case Presentation 1 highlights some important learning points. Musculoskeletal symptoms are a common clinical manifestation of RTA and can be alleviated with the correction of hypokalemia. Secondly, patients who present with kidney stones should be screened for RTA and incomplete distal RTA should be considered in any patients with nephrocalcinosis and a persistent urine pH of at least 5.5 in the absence of urinary tract infection and normal or near-normal serum  $\text{HCO}_3^-$  concentrations. Early treatment of distal RTA also improves nephrocalcinosis symptoms and may prevent recurrence of kidney stones.



## Proximal RTA (Type 2)

### Clinical Case Presentation 2

A 65-year-old man presents with back pain and unexplained anemia. Upon evaluation, the following laboratory values are obtained:  $\text{Na}^+$  139 mmol/L,  $\text{K}^+$  3.4 mmol/L,  $\text{HCO}_3^-$  18 mmol/L,  $\text{Cl}^-$  108 mmol/L, glucose 104 mg/dL, creatinine 2.2 mg/dL, and total protein 10.1 g/dL. An arterial blood gas test shows pH 7.35 and  $\text{pCO}_2$  33 mmHg. The urinalysis shows 1+ glucose and a urine pH of 5.5. The patient is diagnosed with multiple myeloma complicated by evidence of proximal RTA in association with generalized dysfunction of the proximal tubule (Fanconi syndrome).

Isolated proximal type 2 RTA is characterized by defects in the reabsorption of filtered  $\text{HCO}_3^-$  in the proximal tubule without defects in the transport of other solutes (Table 1) [33, 34]. The threshold serum concentration for  $\text{HCO}_3^-$  reabsorption (normally approximately 25 mmol/L) is reduced, leading to delivery of larger quantities of filtered  $\text{HCO}_3^-$  to the distal nephron (which has a low capacity for  $\text{HCO}_3^-$  reabsorption) and urinary  $\text{HCO}_3^-$  wastage [33, 34]. Reductions in serum  $\text{HCO}_3^-$  cause acidosis; however, the urine pH remains alkaline because of the presence of urinary  $\text{HCO}_3^-$  [34]. When serum  $\text{HCO}_3^-$  concentrations decrease below the lower threshold (16–20 mmol/L), a new steady state is reached, whereby all filtered  $\text{HCO}_3^-$  is reabsorbed. At this point, the urine contains no  $\text{HCO}_3^-$  and is maximally acidic [33].

A diagnosis of proximal RTA may be suspected in patients who present with hypokalemia, normal anion gap metabolic acidosis, and acidic urine (pH < 5.5) [7]. Other signs of proximal tubular dysfunction, including hypophosphatemia, hypouricemia, euglycemic glycosuria, and proteinuria, as observed in Clinical Case Presentation 2, are also consistent

with a proximal RTA diagnosis and are reflective of generalized proximal tubular dysfunction [7]. Fractional urinary  $\text{HCO}_3^-$  excretion, which is normally less than 5% of filtered  $\text{HCO}_3^-$ , is usually approximately 15% in patients with proximal RTA [35]. Isolated proximal RTA, that is decreased  $\text{HCO}_3^-$  reabsorption without abnormalities in the transport of other solutes, is rare [34]. The etiology of isolated proximal RTA may be inherited (autosomal recessive mutations in *SLC4A4*, the gene encoding electrogenic NBCe1 [36]) or acquired (e.g., due to carbonic anhydrase inhibitors [34]). Patients with isolated proximal RTA typically present with growth retardation in early childhood [37].

In patients with proximal RTA, hypokalemia develops as a result of the loss of proximal  $\text{HCO}_3^-$  reabsorption [7]. Increased urinary excretion of  $\text{HCO}_3^-$  causes a decrease in intravascular volume, which leads to RAAS stimulation. Impaired proximal  $\text{HCO}_3^-$  reabsorption also causes increased distal  $\text{Na}^+$  delivery. The increase in RAAS activity results in elevated aldosterone levels that, combined with elevated distal  $\text{Na}^+$  concentrations, cause an increase in urinary  $\text{K}^+$  excretion (i.e.,  $\text{K}^+$  wasting) that leads to hypokalemia [7].

Proximal RTA may occur as an isolated defect in  $\text{HCO}_3^-$  reabsorption, but more typically occurs in association with Fanconi syndrome, characterized by a widespread proximal tubular dysfunction resulting in the loss of phosphate, glucose, uric acid, amino acids, and low molecular weight proteins, as well as  $\text{HCO}_3^-$  [33, 34]. Although proximal RTA is not associated with nephrolithiasis or nephrocalcinosis, patients with proximal RTA and Fanconi syndrome may develop skeletal abnormalities, such as osteomalacia [38–41]. Skeletal abnormalities result from impaired phosphate reabsorption, which causes chronic hypophosphatemia due to renal phosphate wasting [7, 38, 41]. Active vitamin D deficiency may be present as a result of impaired conversion of 25(OH) vitamin  $\text{D}_3$  to 1,25 (OH) $_2$  vitamin  $\text{D}_3$  in the proximal tubule [40]. Osteopenia may also be evident as a result of acidosis-induced bone demineralization [42].

Proximal RTA in association with Fanconi syndrome can occur following exposure to some medications, including tenofovir [34],

ifosfamide [43], sodium valproate [44], and topiramate [45]. Topiramate is a carbonic anhydrase inhibitor that can cause simultaneous defects in both proximal and distal acidification mechanisms, presenting as type 3 RTA [46]. Proximal RTA can occur secondary to metabolic diseases, such as hereditary fructose intolerance and glycogen storage disease [47, 48]. As illustrated by Clinical Case Presentation 2, the most common cause of acquired Fanconi syndrome in adults is multiple myeloma [49].

The clinical manifestations of anemia, hypercalcemia, and bone pain suggest a diagnosis of multiple myeloma. The patient's condition is also complicated by proximal RTA, characterized by impaired proximal  $\text{HCO}_3^-$  reabsorption, hypokalemia, and variable urine pH. As the most common cause of proximal RTA in adults is multiple myeloma, this diagnosis should be excluded in all adults with proximal RTA unless another cause is found.

#### Hyperkalemic RTA (Type 4)

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##### Clinical Case Presentation 3

A 55-year-old man with long-standing diabetes is referred for evaluation and treatment of diabetic nephropathy. His only medication is celecoxib 200 mg/day for treatment of mild degenerative joint disease. Physical examination is significant for a blood pressure of 146/92 mmHg and trace pedal edema. Laboratory test results show  $\text{Na}^+$  142 mmol/L,  $\text{K}^+$  5.7 mmol/L,  $\text{Cl}^-$  108 mmol/L,  $\text{HCO}_3^-$  18 mmol/L, serum creatinine 2.0 mg/dL, protein 4.6 g/24 h, and an arterial blood gas test shows pH 7.5 and  $\text{pCO}_2$  33 mmHg. His primary care physician has been reluctant to start either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) because of increased serum  $\text{K}^+$  concentrations.

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Hyperkalemic (type 4) RTA commonly develops in patients with diabetes or interstitial

nephritis and is characterized by a disturbance in distal nephron function, leading to a reduction in the excretion of  $\text{H}^+$  and  $\text{K}^+$  in the cortical collecting duct that results in hyperkalemic, hyperchloremic, normal anion gap acidosis (Table 1) [50, 51]. Patients with hyperkalemic type 4 RTA are often asymptomatic and are typically diagnosed during routine laboratory analyses. When symptomatic, manifestations may include muscle weakness or palpitations due to cardiac arrhythmias [7, 52]. Hyperkalemic RTA may be diagnosed by the presence of hyperkalemia, normal anion gap metabolic acidosis, and abnormal serum aldosterone levels, although the GFR may be near-normal or only moderately reduced (45 to less than 60 mL/min/1.73 m<sup>2</sup>) [7, 8]. As illustrated by Clinical Case Presentation 3, patients usually have diabetes with mild-to-moderate decreases in GFR, a serum  $\text{HCO}_3^-$  concentration of 18–22 mmol/L, and a serum  $\text{K}^+$  concentration of 5.5–6.5 mmol/L [7]. Other causes of hyperkalemia and normal anion gap acidosis include selective aldosterone deficiency, or defects in  $\text{K}^+$  or  $\text{H}^+$  secretion resulting from aldosterone resistance in the kidney (sickle cell nephropathy) [7, 52]. Urinary obstruction can give rise to type 4 RTA [52, 53]. In patients with obstructive uropathy and hyperkalemic metabolic acidosis, those who are unable to acidify their urine pH to less than 5.5 are thought to have a voltage-dependent defect in  $\text{Na}^+$  transport in the distal nephron (i.e., voltage-dependent distal RTA) [52, 53].

Type 4 RTA is typically caused by selective aldosterone deficiency or intrinsic defects in the cortical collecting duct that lead to aldosterone resistance, which causes impaired distal  $\text{H}^+$  and  $\text{K}^+$  secretion [7, 52]. Hypoaldosteronism causes reduced principal cell  $\text{Na}^+$  reabsorption and a decrease in transepithelial voltage in the cortical collecting duct, which results in diminished excretion of  $\text{H}^+$  and  $\text{K}^+$ . Increased serum  $\text{K}^+$  concentrations inhibit  $\text{NH}_3$  synthesis in the proximal tubule, further reducing the kidney's capacity to excrete acid. As described above,  $\text{NH}_3$  availability is critical for normal distal  $\text{H}^+$  secretion. Lack of adequate  $\text{NH}_3$  buffer results in a drop in urine pH creating a steep pH gradient, which impedes distal  $\text{H}^+$  secretion. Aldosterone

deficiency can cause  $\text{Na}^+$  wasting, leading to decreased plasma volume that stimulates proximal  $\text{Na}^+$  reabsorption. The reduction in distal  $\text{Na}^+$  delivery secondarily inhibits secretion of  $\text{K}^+$  and  $\text{H}^+$  in the distal nephron [7, 52]. Hyperkalemia reduces  $\text{NH}_3$  production in the proximal tubule and inhibits  $\text{NH}_4^+$  transport in the thick ascending limb as the high luminal  $\text{K}^+$  concentrations compete with  $\text{NH}_4^+$  for  $\text{Na}^+/\text{K}^+ / 2\text{Cl}^-$  cotransporters and apical  $\text{K}^+$  channels [54]. Reductions in urine  $\text{NH}_3$  can be detected by a positive urine anion gap and a failure to increase the urine osmolal gap.

In Clinical Case Presentation 3, the patient's long history of diabetes led to an increased risk for type 4 RTA due to development of hyporeninemic hypoaldosteronism. Renin is suppressed because of salt retention, which causes volume expansion as well as atrophy and suppression of the juxtaglomerular apparatus, which leads to reduced renin secretion [7, 51]. A reduction in renin release or development of aldosterone resistance can be caused by chronic interstitial fibrosis, which commonly develops in CKD, particularly in patients with diabetic kidney disease [52]. Impaired cortical collecting duct function may also occur as a result of kidney structural damage due to interstitial kidney disease or obstructive uropathy [52]. Lupus nephritis is another cause of type 4 RTA due to tubulointerstitial damage and hyporeninemic hypoaldosteronism [55].

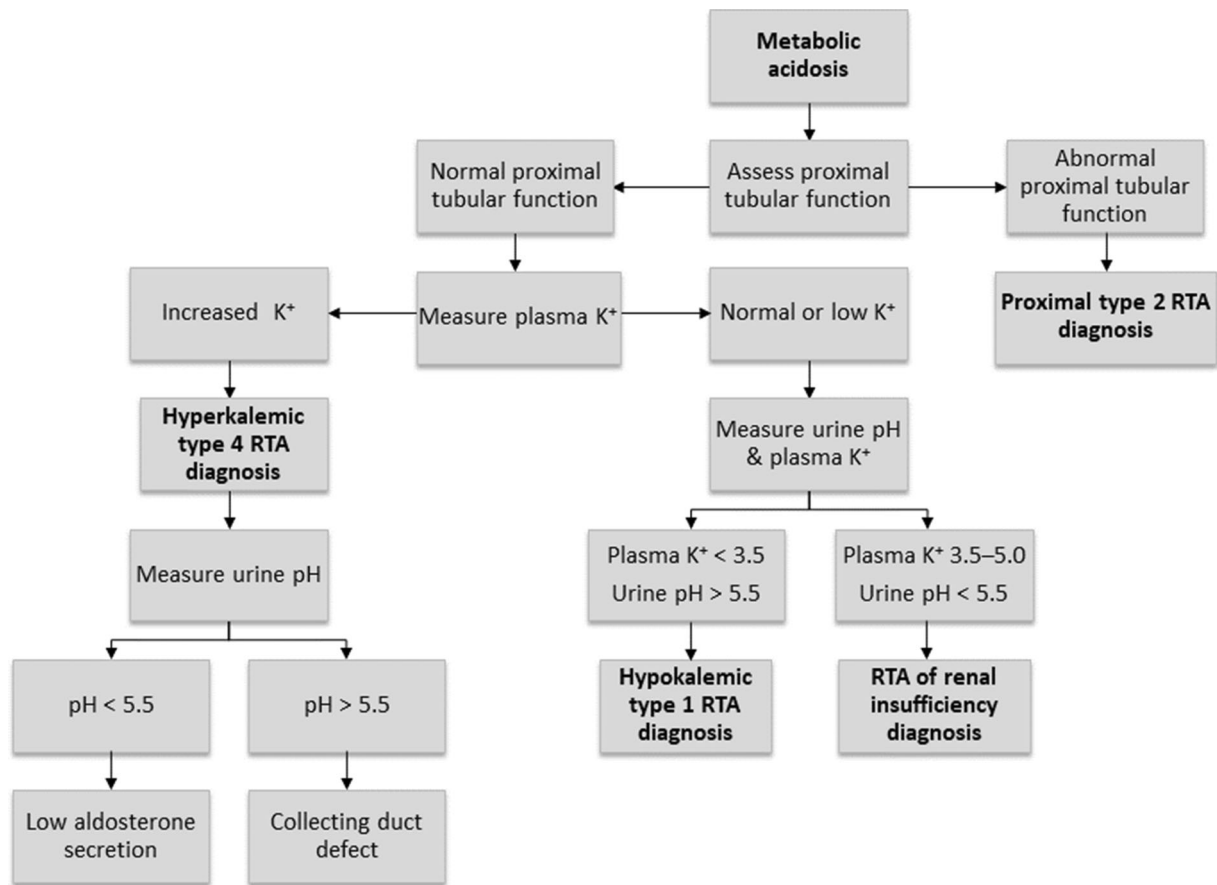
Patients with CKD are also at risk of developing RTA because of the progressive loss of functional kidney mass [7]. Initially, there is an adaptive increase in  $\text{NH}_4^+$  production and acid secretion [56]; however, as kidney impairment progresses (GFR 30–40 mL/min/1.73 m<sup>2</sup>), this adaptive increase is unable to maintain sufficient net  $\text{H}^+$  excretion to keep pace with endogenous acid production. Patients develop a hyperchloremic normal gap acidosis, often referred to as RTA of kidney insufficiency [7]. In patients with more advanced CKD (GFR < 15–20 mL/min/1.73 m<sup>2</sup>), the ability to excrete phosphate and other anions is reduced and a high anion gap metabolic acidosis develops; the acidosis at this stage is termed uremic acidosis. During this transition, patients frequently manifest features of both a normal and

increased anion gap metabolic acidosis [7]. Furthermore, patients with stage 3–5 CKD and hyperkalemia commonly develop metabolic acidosis as progressive kidney impairment leads to compromised maintenance of electrolyte and acid–base balance [57].

Pseudohypoaldosteronism is a genetic condition associated with hyperkalemic, hyperchloremic metabolic acidosis with normal kidney function and either normal or high aldosterone levels [52]. Type 1 pseudohypoaldosteronism may be caused by mutations in genes encoding the mineralocorticoid receptor or ENaC [52], whereas type 2 pseudohypoaldosteronism is caused by mutations in genes encoding the with-no-lysine (WNK) family of kinases [58]. Mutations in ENaC cause  $\text{Na}^+$  wasting and are characterized by increased aldosterone levels, while WNK mutations give rise to  $\text{Na}^+$  retention and either normal or low circulating aldosterone levels [52, 58].

Hyperkalemic type 4 RTA may be caused by medications, including  $\text{K}^+$ -sparing diuretics (e.g., spironolactone, eplerenone, and amiloride), antibiotics (e.g., trimethoprim and pentamidine), nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, ACE inhibitors, and heparin or low molecular weight heparin [5, 59]. These agents cause hyperkalemic RTA by reducing aldosterone synthesis (ACE inhibitors), release (NSAIDs and heparin), or receptor binding (spironolactone, eplerenone), or through inhibition of ENaC (amiloride, trimethoprim, and pentamidine) [5]. Hyperkalemic RTA may also be caused by immunosuppressant therapy with calcineurin inhibitors (e.g., tacrolimus and ciclosporin) [60–62]. Calcineurin inhibitors block  $\text{K}^+$  and  $\text{H}^+$  secretion from the collecting duct through inhibition of basolateral  $\text{Na}^+/\text{K}^+ \text{ - ATPase}$  and  $\text{Na}^+/\text{K}^+ / 2\text{Cl}^-$  cotransporter activity [62, 63]. Calcineurin inhibitors also suppress expression of mineralocorticoid receptors, resulting in aldosterone resistance [64].

Clinical Case Presentation 3 highlights the need to monitor patients with diabetes for development of hyperkalemic RTA. The patient's COX-2 inhibitor therapy potentially contributed to the development of hyperkalemia and should be discontinued. Although



**Fig. 4** A suggested algorithm for diagnosing renal tubular acidosis. Reprinted by permission of Edizioni Minerva Medica from *Minerva Endocrinologica* 2019 December; 44(4):363–77 [7]

treatment with an ACE inhibitor or ARB was avoided because of the patient's refractory hyperkalemia, the patient has diabetic nephropathy and would benefit from use of a RAAS inhibitor to slow the subsequent progression of CKD and to provide cardiovascular protection. Strategies for correction and minimization of hyperkalemia are discussed in the next section.

## CLINICAL MANAGEMENT OF RTA

### Differential Diagnosis of RTA

An approach to diagnosing RTA in a patient who presents with metabolic acidosis is shown

in Fig. 4 [7]. In all cases of metabolic acidosis, plasma or serum anion gap should be the first laboratory assessment; hyperchloremic metabolic acidosis with a normal anion gap is present in all types of RTA (Table 1) [8, 65]. Analysis of urine biochemistry may also be useful in the evaluation of RTA; in patients with hyperchloremic metabolic acidosis and alkaline urine (i.e., pH > 5.5), RTA of some type should be strongly suspected [8].

Confirmatory testing of distal versus proximal RTA involves assessment of the markers of urinary acid and  $\text{HCO}_3^-$  secretion [8]. An  $\text{NH}_4^+$  loading test is used to confirm distal RTA in patients with hypokalemic, hyperchloremic metabolic acidosis and urine pH > 5.5; at 6 h after oral ingestion of  $\text{NH}_4\text{Cl}$  100 mg/kg,

patients with distal RTA will develop a positive urine anion gap (UAG; i.e., urine  $\text{Na}^+$  + urine  $\text{K}^+$  – urine  $\text{Cl}^-$ ) [8]. As the  $\text{NH}_4\text{Cl}$  test is associated with gastrointestinal adverse effects (e.g., nausea and vomiting), the furosemide–fludrocortisone test may be used as an alternative method of diagnosing distal RTA [66, 67].

In patients with distal RTA, measurement of the urine-to-blood (U-B)  $\text{pCO}_2$  gradient during an  $\text{NaHCO}_3$  infusion can be used to diagnose  $\text{H}^+$ -ATPase secretory defect [68]. Patients with an  $\text{H}^+$ -ATPase defect have an abnormally low U-B  $\text{pCO}_2$  gradient (30 mmHg or lower), indicating impaired distal  $\text{H}^+$  secretion [68]. In patients with a gradient defect, as occurs with amphotericin B-induced distal RTA [13], the U-B  $\text{pCO}_2$  gradient is normal (greater than 30 mmHg), suggesting an intact  $\text{H}^+$  secretory mechanism [69]. In these patients, secreted  $\text{H}^+$  diffuses back into the cell as a result of a luminal permeability defect [13].

A diagnosis of proximal RTA may be confirmed using a  $\text{NaHCO}_3$  loading test; during an intravenous infusion of  $\text{NaHCO}_3$ , the increase in serum  $\text{HCO}_3^-$  above the reabsorption threshold will lead to fractional excretion of  $\text{HCO}_3^-$  greater than 15% or urine pH > 7.5 in patients with proximal RTA [8]. Patients with proximal RTA should also be evaluated for Fanconi syndrome by assessment of serum and urine samples for glycosuria, hypophosphatemia, and hypouricemia.

The differential diagnosis of type 4 hyperkalemic RTA may be divided into conditions associated with hypoaldosteronism or those caused by cortical collecting duct defects. A urine pH of less than 5.5 indicates defects caused by impaired aldosterone activity and a more severe reduction in  $\text{NH}_3$  availability than impairment of  $\text{H}^+$  secretion [7]. In contrast, when the primary defect is caused by structural damage to the cortical collecting duct, the urine pH is more alkaline [7]. Selective aldosterone deficiency may be confirmed after other causes of hyperkalemia are excluded, including transcellular shifts in  $\text{K}^+$  or the use of  $\text{KCl}$ ,  $\text{K}^+$ -sparing diuretics, or RAAS inhibitors [52]. After correction of serum  $\text{K}^+$ , persistently low aldosterone levels indicate aldosterone deficiency; in most cases plasma renin levels are low. In

patients with hyperkalemia, urinary  $\text{K}^+$  below 40 mmol/L or fractional  $\text{K}^+$  excretion below 20% are indicative of a defect in kidney  $\text{K}^+$  secretion [52]. In patients with hypoaldosteronism, but normal renin levels, possible causes include adrenal gland damage, Addison disease, critical illness (i.e., direct renal suppression), RAAS inhibitor therapy, or heparin-induced suppression of aldosterone synthesis [50].

Extrarenal conditions may mimic RTA by causing normal gap metabolic acidosis through increased production of endogenous  $\text{H}^+$  and accelerated loss of extrarenal  $\text{HCO}_3^-$  [7]. Extrarenal metabolic acidosis is associated with elevated levels of  $\text{H}^+$  and urinary  $\text{NH}_4^+$  excretion [7]. Severe or chronic diarrhea commonly causes hyperchloremic metabolic acidosis through the loss of large amounts of gastrointestinal  $\text{HCO}_3^-$ , particularly as  $\text{HCO}_3^-$  concentrations are usually higher in diarrheal fluid than in plasma [8, 9]. The reduction in plasma volume triggers an increase in kidney  $\text{NaCl}$  reabsorption which, in combination with  $\text{HCO}_3^-$  losses, leads to normal anion gap metabolic acidosis [7]. Low serum pH, as well as hypokalemia caused by gastrointestinal losses, promotes ammoniogenesis in the proximal tubule; the increased  $\text{NH}_3$  concentrations allow for increased  $\text{H}^+$  excretion by the distal nephron. This can result in an increased urine pH in patients with chronic diarrhea because of increases in kidney  $\text{NH}_3$  metabolism [7]. Chronic laxative abuse has been reported to mimic distal RTA through intestinal losses of  $\text{HCO}_3^-$  and  $\text{K}^+$  [70]. The normal increase in urinary  $\text{NH}_3$  excretion in these situations is reflected by a negative urinary anion gap and an increased urine osmolal gap.

## Treatment of RTA

### *Dietary Considerations*

In general, plant-based diets contain a lower net acid load and less bioavailable phosphate than animal-based diets [71]. In patients with metabolic acidosis, the dietary acid load can be decreased by limiting acid-producing foods (e.g., animal protein) and increasing alkali-producing foods (e.g., fruits and vegetables)

(Table 1) [72–74]. Reduction in the consumption of dietary protein obtained from animal sources also results in increases in serum total CO<sub>2</sub> concentrations [74].

Changes in dietary consumption of citrus fruit and juices, as well as restricted Na<sup>+</sup>, oxalate, fructose, and animal protein intake, in combination with normal calcium intake may also benefit patients with distal RTA and nephrolithiasis [75]. Increased fruit and vegetable intake is associated with increased urinary citrate excretion in patients with hypocitraturia and nephrolithiasis [75, 76]. In patients with hyperkalemic RTA, dietary restriction of K<sup>+</sup> has previously been the standard of care [5]; however, new data suggest that increased intake of alkali-producing fruits and vegetables (which are often high in K<sup>+</sup>) and limiting intake of acid-producing foods may correct acidosis [72].

### Pharmacotherapy

Table 1 summarizes the different pharmacotherapy options for patients with RTA.

Alkali therapy may be used to correct acidosis in patients with distal or proximal RTA [7]. In patients with distal RTA, alkali therapy also corrects for hypokalemia. Alkali therapy with 1–2 mmol/kg/day NaHCO<sub>3</sub> or KHCO<sub>3</sub> is normally sufficient to equal daily acid production [5]; however, in patients with nephrolithiasis or nephrocalcinosis, the elevated Na<sup>+</sup> load with NaHCO<sub>3</sub> therapy may cause increased urine calcium excretion, which can precipitate kidney stone formation. In these patients, K-citrate administration is preferable; this will also increase urine citrate excretion and prevent recurrence of kidney stones [75]. Patients with severe hypokalemia should also receive K<sup>+</sup> replacement (i.e., with KCl or K-citrate) to prevent further lowering of serum K<sup>+</sup> concentrations and symptomatic hypokalemia [7]. Long-term treatment of distal RTA generally requires a combination of NaHCO<sub>3</sub> and KHCO<sub>3</sub> [7, 14]. Children with distal RTA require sufficient NaHCO<sub>3</sub> or KHCO<sub>3</sub> (usually 4–8 mmol/kg/day) to maintain normal serum HCO<sub>3</sub><sup>-</sup> concentrations and prevent growth retardation [5].

In contrast, treatment of proximal RTA is often challenging and patients require larger

quantities of alkali therapy (10–15 mmol/kg/day), which are usually administered as a K<sup>+</sup> salt (e.g., K-citrate) to avoid worsening hypokalemia [5, 7]. However, as exogenous alkali is rapidly excreted in the urine, correction of acidosis is often impossible despite administration of large amounts of alkali therapy [7]. In addition to alkali therapy, patients with Fanconi syndrome are treated with fluid and electrolyte replacement to prevent volume depletion, as well as supplementation with vitamin D and phosphate (1–3 g/day) to prevent bone disease [77]. Impaired proximal HCO<sub>3</sub><sup>-</sup> reabsorption leads to most of the administered HCO<sub>3</sub><sup>-</sup> being lost in the urine with minimal increases in serum concentrations [78], while increased distal Na<sup>+</sup> delivery and elevated aldosterone levels cause increased renal K<sup>+</sup> wasting [7]. Hydrochlorothiazide may be beneficial in increasing HCO<sub>3</sub><sup>-</sup> reabsorption capacity, preventing volume expansion, and increasing the effectiveness of alkali therapy; however, supplemental K<sup>+</sup> or K<sup>+</sup>-sparing diuretics are needed to prevent hypokalemia [5, 77]. After initiation of therapy, patients should be closely monitored for severe electrolyte abnormalities. Children with proximal RTA often require aggressive alkali therapy (5–15 mmol/kg/day) to mitigate bone disease and growth retardation [79], whereas alkali therapy is typically administered in adults with serum HCO<sub>3</sub><sup>-</sup> concentrations of less than 18 mmol/L to prevent severe acidosis [7].

NaHCO<sub>3</sub> therapy is often associated with gastrointestinal adverse effects, most commonly bloating and belching, and should be taken on an empty stomach [72, 74]. If these adverse effects limit patient adherence, Na-citrate or enteric-coated NaHCO<sub>3</sub> (where available) may be considered [74].

In patients with hyperkalemic type 4 RTA, lowering of serum K<sup>+</sup> concentrations often leads to correction of metabolic acidosis [7]. The reduction in serum K<sup>+</sup> leads to increased NH<sub>3</sub> production in the proximal tubule and medullary transfer, thereby increasing the availability of buffer supply for distal acidification [7]. Any non-essential medications affecting renal K<sup>+</sup> excretion or aldosterone synthesis or activity should be discontinued [5, 7]. In Clinical Case

Presentation 3 described above, discontinuation of the COX-2 inhibitor celecoxib would be beneficial in reducing serum  $K^+$  concentrations. ACE inhibitors and ARBs reduce urinary  $K^+$  excretion through inhibition of aldosterone secretion in the adrenal gland and may cause hyperkalemia in patients with pre-existing conditions that cause impaired  $K^+$  excretion [80]. For this reason, RAAS inhibitor therapy was avoided in Clinical Case Presentation 3; however, ACE inhibitors and ARBs are normally continued in patients with CKD because of their cardiovascular and renoprotective benefits [7]. Low-dose fludrocortisone therapy may also be effective in managing hyperkalemia and hyponatremia in patients with type 4 RTA who do not have heart failure or hypertension [52, 81]. Since thiazide diuretics are largely ineffective in patients with an estimated GFR of less than 30 mL/min/1.73 m<sup>2</sup>, loop diuretics and NaHCO<sub>3</sub> therapy may be beneficial in patients with type 4 RTA, particularly when fludrocortisone is not tolerated. Loop diuretics may reduce serum  $K^+$  and help control volume overload by increasing Na<sup>+</sup> delivery and flow rates to the cortical collecting duct while lowering blood pressure [52]. The Kidney Disease-Improving Global Outcomes guidelines suggest administration of oral HCO<sub>3</sub><sup>-</sup> therapy to maintain serum HCO<sub>3</sub><sup>-</sup> in the normal range in patients with CKD and serum HCO<sub>3</sub><sup>-</sup> less than 22 mmol/L [82]. NaHCO<sub>3</sub> administration will correct metabolic acidosis and further minimize the risk of hyperkalemia, and the addition of Na<sup>+</sup> would not be problematic in the setting of effective diuretic therapy. However, patients on NaHCO<sub>3</sub> therapy should be closely monitored for volume overload and hypertension [7].

### **Novel Pharmacotherapy**

For patients with hyperkalemic type 4 RTA, there are newer  $K^+$ -binding agents available (i.e., patiromer and sodium zirconium cyclosilicate [SZC]), which can be used to treat hyperkalemia and improve acidosis. Patiromer is a polymeric cation exchange resin that binds  $K^+$  ions in exchange for calcium ions in the colon [83], whereas SZC is non-polymeric, selective  $K^+$ -binder, which entraps  $K^+$  and NH<sub>4</sub><sup>+</sup> ions in exchange for H<sup>+</sup> and Na<sup>+</sup> ions throughout the

gastrointestinal tract [84]. Both patiromer and SZC are effective in patients receiving RAAS inhibitor therapy, which allows continuation of these therapeutic agents in the presence of hyperkalemia [85, 86]. SZC has also been associated with significant increases in serum HCO<sub>3</sub><sup>-</sup> concentrations by approximately 2 mmol/L versus placebo during the initial 48-h treatment period and 2–3 mmol/L during maintenance therapy for 1 month, regardless of CKD stage [85]. This increase in serum HCO<sub>3</sub><sup>-</sup> with SZC is most likely as a result of gastrointestinal NH<sub>4</sub><sup>+</sup> binding ions and associated decreases in serum urea concentrations [87]. Reducing serum  $K^+$  concentrations with secondary increases in NH<sub>3</sub> synthesis may be an additional mechanism by which acidosis is improved with SZC. Whether patiromer produces similar effects on serum HCO<sub>3</sub><sup>-</sup> remains to be determined; however, treatment with SZC may provide therapeutic benefits in patients with hyperkalemic RTA. Studies are needed to confirm the efficacy and safety of SZC or patiromer in hyperkalemic RTA.

Veverimer (TRC101) is a treatment for metabolic acidosis currently in clinical development. Veverimer selectively binds H<sup>+</sup> in the gastrointestinal tract, thereby increasing serum HCO<sub>3</sub><sup>-</sup> concentrations and correcting acidosis [88]. In patients with CKD and metabolic acidosis, veverimer significantly increased serum HCO<sub>3</sub><sup>-</sup> concentrations within 24–72 h of administration and continued to be effective over 2 weeks [89] or 12 weeks [90]. In a 1-year extension study, veverimer therapy corrected metabolic acidosis, was well tolerated, and was associated with improved patient-reported physical function outcomes [88]. Although studies in patients with RTA are needed to confirm the efficacy and safety of veverimer in RTA, this drug represents an emerging alternative to alkali therapy.

## **CONCLUSIONS**

In clinical practice, patients with RTA can present with a wide range of signs and symptoms. Accurate diagnosis of RTA is important in selecting the appropriate treatment strategy.

Diet modifications and alkali therapy are treatment options, and the availability of newer K<sup>+</sup> binders may assist in the management of hyperkalemic RTA. The H<sup>+</sup>-binding agent veverimer may be an additional emerging treatment option.

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