Renal Tubular Acidosis

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KEYWORDS

• Acid–base homeostasis • Bicarbonate • Renal Fanconi syndrome • Hyperkalemia • Nephrocalcinosis • Ammonium • Urine anion gap

KEY POINTS

- Renal tubular acidosis should be suspected in poorly thriving young children with hyperchloremic and hypokalemic (in case of renal tubular acidosis types 1–3) normal anion gap metabolic acidosis, with or without syndromic features.
- Further workup is needed to determine the type of renal tubular acidosis and the presumed etiopathogenesis (eg, genetic forms, drug-induced, or secondary to autoimmune disorders), which will inform the treatment choices and prognosis.
- The risk of nephrolithiasis and calcinosis is linked to the presence (proximal renal tubular acidosis, negligible stone risk) or absence (distal renal tubular acidosis, high stone risk) of urine citrate excretion.

INTRODUCTION

The acid–base status is tightly controlled in the human body. Any deviation affects the physiologic milieu of cellular membranes, intracellular signaling, and metabolism, resulting in acute and long-term consequences on the cardiovascular system, bone health, and other tissue functions. A key player in the maintenance of acid–base homeostasis are the kidneys. The term renal tubular acidosis (RTA) describes a group of disorders caused by defects in the molecular machinery of the renal tubules that facilitates the reabsorption of bicarbonate (HCO_3^-), the secretion of protons (H^+), or both.[1]

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An adult consuming a normal western diet generates about 1 mmol of H^+ per kilogram of body weight that needs to be disposed of in a regulated fashion; the amount is 2 to 3 mmol per kilogram of body weight in growing children.[2–4] The kidney ensures whole body HCO_3^- homeostasis by producing HCO_3^- de novo from metabolizable organic anions, primarily in the proximal tubule, but also in other nephron segments. The generation of 2 NH_4^+ in the proximal tubule results in the release 2 NH_4^+.[5] Physiologically, NH_4^+ is partitioned so that about 50% end up in the circulation (renal vein) and the other 50% in the lumen, which undergoes recycling. Intraluminal ammonia binds and excretes hydrogen ions in the form of ammonium. Disturbances of these regulatory mechanisms by mutations of critical transporter molecules, nephro (tubulo) toxic agents or urinary tract obstruction can lead to distinct acid–base imbalances and their long-term clinical consequences, summarily known as RTA.

PHYSIOLOGY OF ACID–BASE REGULATION WITH EMPHASIS ON THE ROLE OF THE KIDNEY

Regulation of Acid–Base Homeostasis

A consequence of performing metabolic work is the generation of protons (H^+). Biological systems function optimally at a narrow pH range. It is, therefore, necessary for an organism to eliminate H^+ to maintain this homeostasis. Mammals, including humans, have adopted 3 general mechanisms to maintain the pH within this narrow physiologic range. The first is to produce and maintain an adequate supply of buffer, both within and outside of cells. The most important intracellular buffers are phosphate and proteins. The major extracellular buffer is bicarbonate. However, mineral bone is composed of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), which can contribute buffer under acidotic conditions. The second mechanism regulating pH is respiration. Bicarbonate is in equilibrium with carbon dioxide and water ($HCO_3^- + H^+ \leftarrow \rightarrow H_2O + CO_2$); both of the substances on the right side of the equilibrium are expelled via the lungs. Consequently, alterations in respiration rapidly adjust plasma pH. Finally, the kidney eliminates protons directly in the urine, but also serves to generate new bicarbonate and to prevent it from being lost in the urine. These processes are outlined elsewhere in this article.

Proximal Renal Tubule and Bicarbonate Reabsorption

Bicarbonate is freely filtered at the glomerulus and must be reabsorbed to prevent its loss in the urine. The majority of bicarbonate is reabsorbed from the proximal tubule. This process depends on the secretion of acid into the proximal tubular lumen. The majority of protons are extruded in exchange for a sodium ion via the epithelial (apical) sodium proton (hydrogen) exchanger[6] isoform 3 (NHE3). A smaller quantity of protons is extruded into the lumen of this segment via a plasma membrane H^+ATPase.[7] Importantly in neonates and potentially older animals,[8] sodium proton exchange in the proximal tubule can also be mediated by NHE8, although this does not completely compensate for the loss of NHE3. The luminal conversion of H^+ and HCO_3^- into CO_2 and H_2O is facilitated by carbonic anhydrase 4 (CA4).[9,10]

$$H_+ + HCO_3 \rightleftarrows H_2CO_3 \underset{CA2}{\overset{CA4}{\rightleftarrows}} H_2O + CO_2$$

Water is then reabsorbed through aquaporin-1, which is expressed in the luminal and basolateral membrane of the proximal tubular cells.[8,11] Carbon dioxide does not require a protein transport mechanism to move across the cells; it is noteworthy, however, that aquaporin-1 has also been reported to facilitate transmembrane CO_2

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movement.[12,13] Cytosolic carbonic anhydrase 2 (CA2) catalyzes intracellular H_2O and CO_2 back into a H^+ and HCO_3^-.[14,15] The proton is recycled across the apical membrane, whereas HCO_3^- is extruded together with Na^+ across the basolateral membrane via the electrogenic sodium bicarbonate cotransporter NBCe1 (solute linked carrier 4 A4; encoded by *SLC4A4*)[16–18] (**Fig. 1**). Bicarbonate escaping the proximal tubule[19] can be reclaimed by the thick ascending limb via a similar process involving NHE3.

Distal Nephron and Acid Secretion

Acid (proton) secretion occurs from type A (alpha) intercalated cells in the connecting tubule and collecting duct. Its secretion is mediated by the apically expressed plasma membrane H^+ATPase. H^+ is generated in the cytosol via conversion of H_2O and CO_2 into a proton and bicarbonate, a process catalyzed by carbonic anhydrase isoform 2, CA2.[15,20] This de novo–generated bicarbonate leaves the cell via the anion exchanger 1 (AE1, gene name *SLC4A1*) in the basolateral membrane.[21,22] Consequently, not only is acid extruded, but base is also generated via this process. H^+ is "trapped" in the

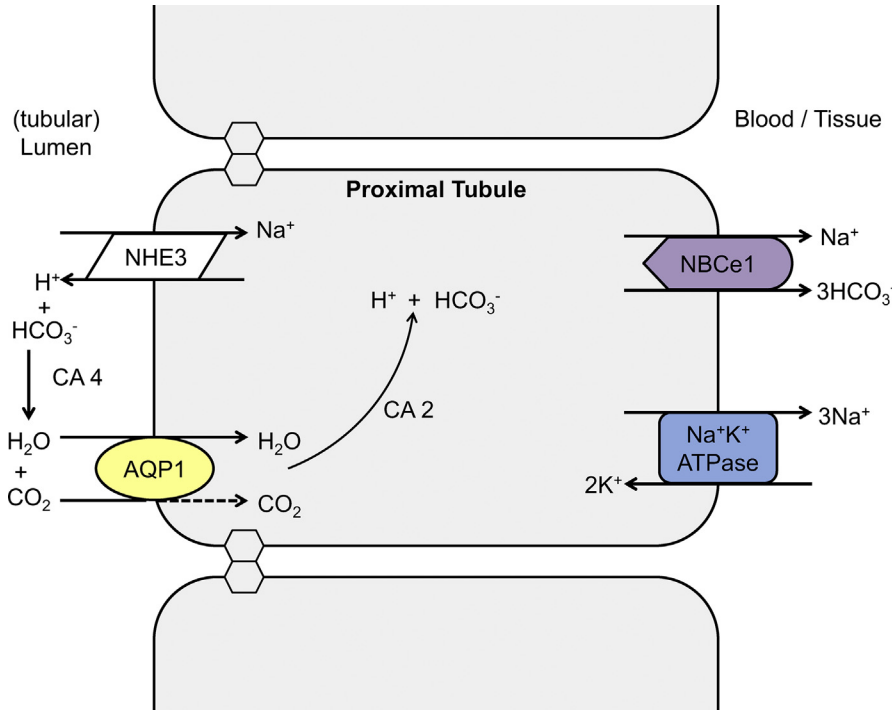

Fig. 1. Proximal tubule reabsorption of bicarbonate. The majority of filtered bicarbonate (HCO_3^-) is reabsorbed from the proximal tubule. It is first enzymatically converted to water and carbon dioxide (CO_2) by carbonic anhydrase 4 (CA4). The proton (H^+) is provided in exchange for sodium (Na^+) by the sodium protein exchanger isoform 3 (NHE3). Intracellular (cytosolic) CA2 converts water and CO_2 back into a proton, which is recycled via NHE3, and bicarbonate is extruded across the basolateral membrane of the cell, back into the circulation via the sodium bicarbonate cotransporter 1 (NBCe1). AQP1, aquaporin-1. (*Adapted from* Alexander RT, Bockenhauer D. Renal tubular acidosis. In: Geary DF, Schaefer F, editors. Pediatric kidney disease. Berlin: Springer; 2016. p. 973–91.)

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lumen of the collecting duct through binding with ammonia (NH_3) to generate ammonium (NH_4^+)[19] (Fig. 2).

This buffering process is essential to maximize urinary acid excretion. Ammonia is concentrated in the lumen of the collecting duct via a recycling mechanism.[23] It is first generated from glutamine in the mitochondria of the proximal tubule and extruded into

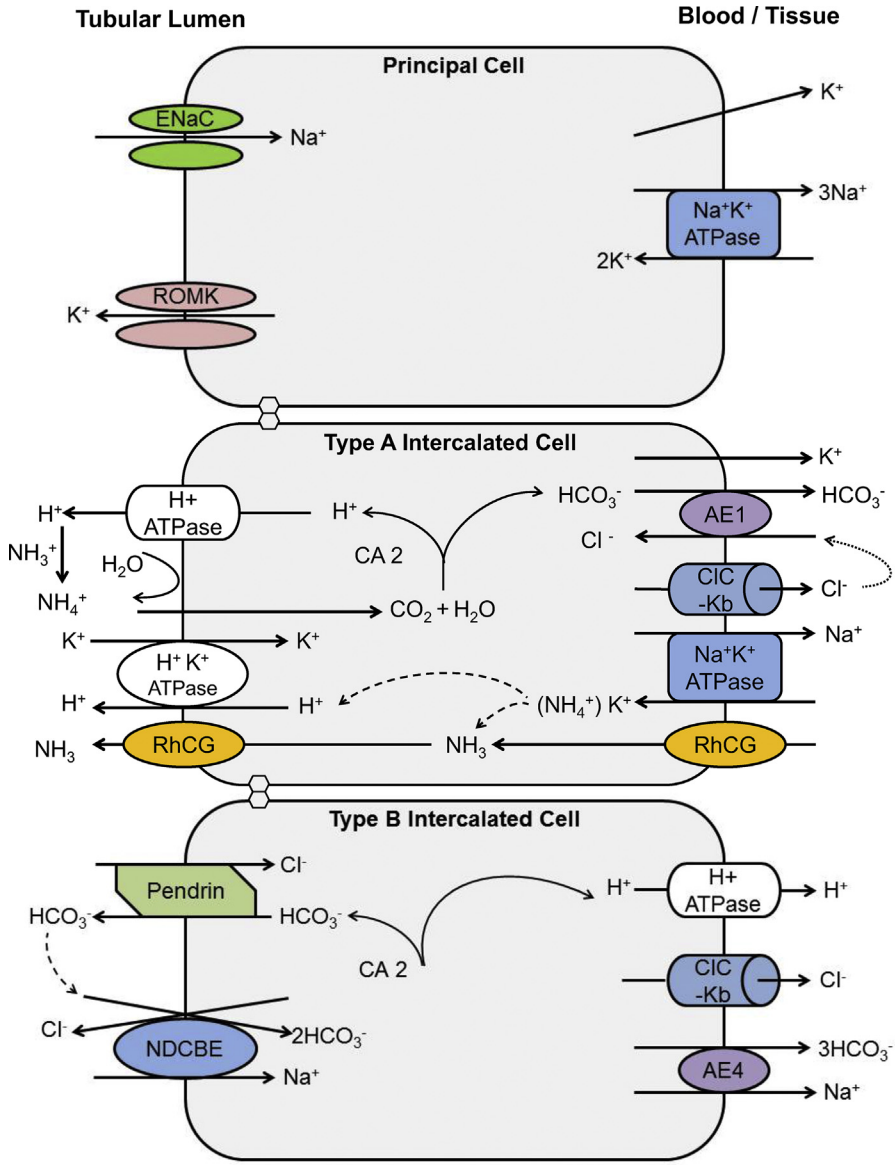

Fig. 2. Acid secretion in the collecting duct (CCD). Epithelial cells are depicted with their major physiologic roles in sodium, potassium, and acid–base regulation. AE1, anion exchanger 1 (SLC4A1); AE4, anion exchanger 4 (SLC4A9); ClC-Kb, chloride channel Kb; ENaC, epithelial sodium channel; NDCBE, sodium-driven chloride/bicarbonate exchanger; RhCG, Rhesus family C glycoprotein; ROMK, renal outer medullary potassium channel.

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the tubular lumen via a sodium proton exchange mechanism.[24,25] This process also generates bicarbonate de novo. Luminal ammonium is absorbed across the epithelial cells in the loop of Henle and concentrated in the medullary interstitium.[26] Ammonia can then diffuse into the lumen of the collecting duct, down its concentration gradient, a process mediated by the Rhesus family C glycoprotein, a relative of the red blood cell antigen,[23] and combine with secreted protons to form ammonium (see **Fig. 2**).

CLINICAL MANIFESTATIONS AND BIOCHEMICAL FEATURES

Distal Renal Tubular Acidosis (Type 1 Renal Tubular Acidosis)

Type 1 (distal) RTA (dRTA) was the first form of RTA described.[1] It was reported as a clinical entity in 1935[27]; the designation as dRTA followed in 1951.[1,28] As the names imply, this tubular disorder is owing to the failure to secrete protons from type A intercalated cells in the connecting tubule and collecting duct.[1] It can be caused by several conditions including single gene defects, autoimmune diseases, such as Sjögren syndrome, drugs, or systemic disorders.[1,29–32] Drugs implicated in causing type 1 RTA include amphotericin B, vanadate, ifosfamide, lithium, and foscarnet. Distal RTA has also been seen in association with primary hyperparathyroidism and medullary sponge kidney (**Box 1**).[33] In (young) children presenting with type 1 RTA, single gene defects should be considered. Not surprisingly, given its requirement for the acidification of urine, mutations in 2 of the subunits of the plasma membrane H^+ATPase, α4 (gene name *ATPV0A4*) and β1 (gene name *ATPV1B1*) or the anion exchanger isoform 1, AE1 (gene name *SLC4A1*) can cause isolated dRTA.[34–40] Mutation in carbonic anhydrase isoform 2 (gene name *CA2*) results in a mixed picture of both proximal renal tubular acidosis (pRTA) and dRTA.[14]

Children with genetic forms of dRTA present with failure to thrive and/or complications of the metabolic abnormalities caused by the disease. Blood tests typically demonstrate a normal anion gap metabolic acidosis (**Box 2**), often with hypokalemia.[41] These children have an inappropriately alkaline urine despite an acidic blood pH. dRTA is also commonly associated with hypercalciuria, nephrocalcinosis and/or nephrolithiasis (reviewed in[42]). Therefore, evaluation of pediatric kidney stone formers should include a blood gas analysis. Autosomal-recessive forms of dRTA are due to mutations in *ATP6V1B1* or *ATP6V0A4* that encode the β1 and α4 subunits of the apical (vacuolar) H^+ ATPase.[40] These proteins are also expressed in the cochlea and endolymphatic sac of the ear.[37] Consequently, children with a mutation in either subunit suffer from sensorineural hearing loss.[37,40,43] Audiometry results may point to the molecular diagnosis and guide genetic testing. The described genetic defect can lead to distinct endolymphatic sac enlargement that can be recognized by an MRI of the inner ear.[44] Mutations of AE1 cause autosomal dominant or recessive dRTA.[35,45,46] A slightly longer isoform of AE1 is expressed in red blood cells. Owing to differential processing in red blood cells and type A intercalated cells, mutations in *AE1* typically cause only one disease or the other.[45] Patients with autosomal-dominant AE1 mutations tend to present later (ie, in adolescence or adulthood) and with less severe hypokalemia than those with autosomal recessive mutations; the latter are less common, cause more severe disease, and are more likely to be associated with hemolytic anemia.[47,48]

Autosomal-dominant mutations of AE1 can also underlie incomplete dRTA,[47] a term that describes individuals with normal acid–base status under physiologic conditions, but an inability to appropriately acidify their urine after an acid load. It

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Box 1
Etiologies of distal (type 1) RTA

Primary/hereditary distal renal tubular acidosis (see Table 1)
Genetic abnormalities of the (apical) H^+ ATPase subunits
Variants of the gene encoding the (basolateral) anion exchanger 1 (AE1)
Variants of the gene encoding the cytosolic carbonic anhydrase 2
Autoimmune disorders
Sjögren syndrome
Lupus erythematosus
Autoimmune hepatitis
Rheumatoid arthritis
Polyarteritis nodosa
Nephrotoxic medications
Amphotericin B
Lithium, mercury
Trimethoprim
Ifosfamide
Vanadate
Foscarnet
Nonsteroidal analgesics
Hypercalciuria/nephrocalcinosis
Primary hyperparathyroidism
Hypothyroidism
Medullary sponge kidney
Tubular interstitial disorders
Obstructive uropathy
Pyelonephritis
Interstitial nephritis
Sickle cell disease
Others
Human immunodeficiency virus-associated nephropathy
Sarcoidosis
Amyloidosis

typically requires an ammonium chloride challenge or furosemide test to make this diagnosis.[31] Interestingly, patients with incomplete dRTA may also present with kidney stones, and dRTA should be considered in the differential diagnosis of hypercalciuria and nephrolithiasis.[36,45,49] Only recently have heterozygous mutations of the H^+ATPase β1 and α4 subunits been associated with incomplete dRTA[50,51] (**Table 1**).

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Box 2
Serum anion gap

The ionic balance is generally tightly regulated. For example, the loss of the anion bicarbonate leads to the displacement of chloride into the extracellular compartment.[127]

The serum anion gap is calculated to estimate the concentrations of active ions using serum sodium, chloride and bicarbonate measurements that are readily available in clinical laboratories. Various components are not directly measured; hence the equation does not result in 0. The "gap" reflects unmeasured anions.

$$\text{Serum anion gap} = Na^+ - (HCO_3^- + Cl^-)$$

A normal serum anion gap is 12 to 16 mmol/L. The serum anion gap is increased in the presence of (unmeasured) ketones, lactate, salicylate, methanol, and so on.

Proximal Renal Tubular Acidosis (Type 2 Renal Tubular Acidosis)

Type 2 or pRTA is caused by a defect in proximal tubular bicarbonate reabsorption. Bicarbonate loss in the urine results in a normal anion gap metabolic acidosis. Hypokalemia is also present, similar to dRTA. However, distal acidification mechanisms remain in place allowing the patient to produce an acidic urine, that is, a urine pH of less than 5.5, when plasma bicarbonate concentrations are below the tubular reabsorption threshold. In contrast with distal tubular acidosis, patients with isolated pRTA do not develop nephrocalcinosis or kidney stones, likely because proximal citrate reabsorption is inhibited by alkaline luminal pH, which ensures sufficient urinary citrate excretion.[42,52–54]

Isolated pRTA is rare. The only known genetic abnormality underlying this disorder are mutations in the sodium bicarbonate cotransporter 1 (NBCe1, gene name *SLC4A4*). Children with this condition also have ocular abnormalities, such as band cataract, glaucoma, or band keratopathy[52,53,55,56] (see **Table 1**).

pRTA is more commonly seen as part of the renal Fanconi syndrome. The latter refers to a disorder of global proximal tubular dysfunction characterized by hypophosphatemia, glucosuria, low molecular weight proteinuria and amino aciduria in addition to (proximal) tubular acidosis. Examples of genetic diseases with prominent pRTA are nephropathic cystinosis, Lowe syndrome. and others, usually with a plethora of additional pathologies.[57,58] Acquired conditions include exposure to ifosfamide, cisplatin, and other tubulotoxic medications[59,60] (**Box 3**).

Combined (Mixed) Renal Tubular Acidosis (Type 3 Renal Tubular Acidosis)

Type 3 RTA combines clinical features of proximal and dRTA. It is a rare autosomal-recessive disorder that manifests with osteopetrosis, cerebral calcifications, nephrocalcinosis and nephrolithiasis, facial dysmorphism (hypertelorism, low set ears, and a depressed nasal bridge), conductive hearing loss and cognitive impairment.[61–64] The only known cause of this disease is a mutation in CA2.[14,65] The role of CA2 in proximal tubule bicarbonate absorption and in distal proton secretion accounts for the combined types of metabolic acidosis. CA2 is essential for osteoclast function, hence the overmineralization, that is, osteopetrosis.

Renal Tubular Acidosis with Hyperkalemia (Type 4 Renal Tubular Acidosis)

In contrast with RTA types 1 to 3, the defining feature of type 4 RTA is a high normal or increased plasma potassium level, not hypokalemia. Affected patients also have a normal anion gap metabolic acidosis. The primary abnormality is actual or effective hypoaldosteronism.[66] It results in sodium wasting from the collecting duct. Because

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Table 1
Genetic causes of RTA

Protein Name	Gene Name	MIM #	Inheritance	Typical Clinical Features	Type of RTA
NBCe1	*SLC4A4*	603345, 604278	AR	Glaucoma, cataracts, band keratopathy	pRTA (type 2)
AE1	*SLC4A1*	109270, 179800, 611590	AD (less commonly AR)	Nephrocalcinosis, osteomalacia, rarely hemolytic anemia	dRTA (type 1)
β1 subunit of the H^+ATPase	*ATP6V1B1*	267300	AR	Sensorineural hearing loss, nephrocalcinosis or nephrolithiasis	dRTA (type 1)
α4 subunit of the H^+ATPase	*ATP6V0A4*	602722, 605239	AR	Late-onset sensorineural hearing loss, nephrocalcinosis or nephrolithiasis	dRTA (type 1)
CA2	*CA2*	611492, 259730	AR	Osteopetrosis	Combined distal/proximal RTA (type 3)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; *ATP6V0A4*, ATPase H + transporting V0 subunit A4; *ATP6V1B1*, ATPase H + transporting V1 subunit B1; CA2, *carbonic* anhydrase 2; dRTA, distal renal tubular acidosis; NBCe1, sodium bicarbonate cotransporter 1; RTA, renal tubular acidosis; SLC, solute-linked carrier.

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Box 3
Etiologies of proximal (type 2) renal tubular acidosis

Isolated (primary) proximal renal tubular acidosis (see also Table 1)

Variants of the gene encoding the (basolateral) proximal tubular sodium bicarbonate cotransporter sodium bicarbonate cotransporter 1[a]

Inherited disorders with (secondary) Fanconi syndrome

Cystinosis

Lowe syndrome

Wilson disease

Autoimmune disorders

Sjögren syndrome

Nephrotoxic medications

Ifosfamide

Cisplatin

Topiramate

Valproate

Acetazolamide

Aminoglycosides

Tetracyclines

Lead

Tubular interstitial disorders

Obstructive uropathy

Medullary cystic kidney disease

Others

Hypocalcemia

Amyloidosis

Multiple myeloma

Monoclonal gammopathy

Light chain deposition disease

[a] Associated with glaucoma, cataracts, or band keratopathy.

potassium and proton secretion in the collecting duct is coupled in this part of the nephron to sodium reabsorption (mainly via the principal cells), type 4 RTA results in hyperkalemic acidosis. Sodium reabsorption in the collecting duct occurs mainly through the aldosterone-regulated epithelial sodium channel ENaC. Normal ENaC function results in a lumen negative membrane potential that is, attenuated both by potassium secretion (through the renal outer medullary potassium channel) and by proton secretion by the plasma membrane H^+ATPase. Consequently, a failure to reabsorb sodium from the collecting duct also prevents H^+ secretion leading to metabolic acidosis (see Fig. 2).

A wide variety of conditions has been implicated in type 4 RTA in childhood.[31] The distally active diuretics spironolactone, amiloride, and triamterene cause RTA through

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their effects on collecting duct principal cells. Spironolactone and triamterene block (or compete with) the mineralocorticoid receptor leading to diminished ENaC expression, whereas amiloride blocks ENaC directly.[67] Type 4 RTA is also observed in patients with obstructive uropathy, pyelonephritis and, occasionally, lupus nephritis (**Box 4**). Genetic forms of hyperkalemic (type 4) RTA are known as pseudo-hypoaldosteronism because the plasma and urine electrolyte pattern resemble absence of aldosterone. Nevertheless, these patients typically present with increased serum aldosterone (and renin) concentrations.[68]

Box 4
Etiologies of hyperkalemic (type 4) renal tubular acidosis

Renal genetic causes

Variants of genes encoding proteins involved in the regulation of the epithelial sodium channel, including the mineralocorticoid receptor and intracellular signaling molecules

Bartter syndrome type 2

Adrenal insufficiency

Congenital adrenal hyperplasia (21-hydroxylase deficiency)

Adrenal suppression (hypoxia, sepsis)

Autoimmune adrenalitis

Addison disease

Autoimmune/related disorders

Lupus nephritis

Renal amyloidosis

Medication induced

Amiloride

Spironolactone

Triamterene

Eplerenone

Angiotensin-converting enzyme inhibitors

Angiotensin receptor blockers

Prostaglandin inhibitors

Calcineurin inhibitors (cyclosporine A, tacrolimus)

Nonsteroidal anti-inflammatory drugs

Heparin

Trimethoprim

Intrinsic renal disease

Chronic kidney disease

Obstructive uropathy

Pyelonephritis

Interstitial nephritis

Kidney transplant

This list is not comprehensive; association with various other diseases have been reported.

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Type 1 pseudohypoaldosteronism is due to mineralocorticoid resistance. Patients display low blood pressure, hyponatremia, and hyperkalemia. There are 2 clinically distinct subtypes. The milder version is inherited as an autosomal-dominant condition and is due to loss of function mutations in the mineralocorticoid receptor gene *NR3C2*.[69,70] The more severe form is inherited as an autosomal-dominant disease. It is caused by mutations in 1 of the 3 ENaC subunits, either alpha, beta, or gamma,[71–74] and affects multiple tissues resulting in increased sodium concentration of sweat, saliva, and airway secretions. This has led at times to the erroneous diagnosis of cystic fibrosis.

Pseudohypoaldosteronism type II, also known as Gordon's syndrome, is a disorder characterized by hypertension and hyperkalemic RTA. Patients with this diagnosis have chloride-dependent sodium retention, and hypertension that is, very sensitive to thiazide therapy.[75] Thiazides inhibit sodium reabsorption through the sodium chloride cotransporter (NCC) in the distal convoluted tubule, upstream from the collecting duct. The pathogenesis of this disease involves increased sodium and chloride reabsorption from the distal convoluted tubule via NCC. Mutations in a number of genes including *WNK1*, *WNK4*, *KLHL3*, and *CUL3* have been identified in patients with this condition.[76–79] The encoded proteins have all been implicated in the regulation of NCC activity or expression. The described mutations cause the stimulation NCC or prevention of its degradation, leading to increased sodium reabsorption from the distal convoluted tubule, volume expansion, and hypertension.[31] This process inhibits sodium reabsorption from the collecting duct and consequently potassium and proton excretion, that is, a hyperkalemic metabolic acidosis.

ACIDOSIS AND URINARY CALCIUM EXCRETION

Effect of Acidosis on Bone

Both acute and chronic metabolic acidosis (such as RTA) cause increased urinary calcium excretion. This is not likely due to increased intestinal calcium absorption, but a result of direct effects on bone.[80,81] There is an acute physiochemical effect and a more chronic cellular response. Bone is covered with negatively charged sites that bind both sodium and potassium. Protons can be exchanged acutely with these monovalent cations. Protons can rapidly dissolve hydroxyapatite and thereby buffer plasma pH and release calcium into blood and the urine.[82,83] Prolonged ($\geq$24 h) exposure to acid inhibits osteoblast and stimulates osteoclast activity,[84–86] which results in further calcium release from bone and calciuria.

Effect of Acidosis on the Renal Tubule

Metabolic acidosis causes calciuria via 2 mechanisms: the first is dissolution of bone and release of calcium into the circulation. This process results in increased glomerular filtration and decreased tubular reabsorption of calcium through feedback inhibition by elevated plasma calcium levels on the tubule (for a review, see[87]). The second mechanism is a direct effect of low cellular pH in the distal nephron. Although filtered calcium is reabsorbed predominantly from the proximal tubule and the thick ascending limb by a passive paracellular process, the ultimate amount of urinary calcium excretion is finely regulated in the distal convoluted and connecting tubule. This process occurs via an active transcellular process mediated by apical calcium influx through the calcium channel TRPV5.[88] Metabolic acidosis decreases calcium reabsorption from the distal nephron via decreasing TRPV5 expression.[89–92] Studies in TRPV5 knockout mice suggest that acidosis (ie, increased distal tubular cytosolic pH) directly impairs distal transcellular calcium reabsorption.[92]

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Renal Tubular Acidosis and Urinary Calcium Excretion

Given the previous discussion, patients with type 2 RTA would be expected to develop hypercalciuria, nephrolithiasis, and nephrocalcinosis as is observed in patients with type 1 RTA.[93] This is not, however, the case. This seeming discrepancy has been explained in part by the differences in urinary citrate excretion.[42] Citrate binds calcium and prevents it from precipitating as a calcium oxalate or calcium phosphate salt. A luminal alkaline pH found in RTA type 2 patients inhibits proximal tubular citrate reabsorption, which enhances the urinary excretion of citrate.[94] Patients with pRTA thus have increased urinary citrate, which might prevent the precipitation of calcium along the tubule. Moreover, increased luminal pH in the distal nephron might also enhance TRPV5 activity resulting in increased calcium reabsorption and decreased urinary calcium excretion.[95]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSES OF RENAL TUBULAR ACIDOSIS

The presence of hypokalemic hyperchloremic metabolic acidosis and a normal plasma anion gap in a patient with a normal glomerular filtration rate are suggestive of RTA. A similar electrolyte constellation can be seen in patients with gastrointestinal bicarbonate losses, for example, owing to profuse watery diarrhea, pancreatic fistula, nasojejunal suctioning, or chronic laxative use. Children with RTA may present with poor growth, volume depletion, fatigue, or lethargy. Alternatively, RTA may be diagnosed incidentally owing to an abnormal blood gas analysis.[96]

Distal Renal Tubular Acidosis

Type 1 RTA is defined by the inability of the distal tubular segments to adequately acidify the urine, which leads to inappropriately alkalized urine in the presence of metabolic acidosis. Patients typically present with hyperchloremic normal serum anion gap metabolic acidosis and hypokalemia, hypercalciuria, and normal glomerular filtration rate. Patients may also demonstrate nephrocalcinosis. The key feature of dRTA is the inability of the kidney to excrete protons as ammonium (NH_4^+). Some authors suggest that the ammonium excretion be used for the classification of RTAs.[97] Hypokalemia of dRTA is partly due to increased secretion through the apical renal outer medullary potassium channel to support ENaC mediated Na^+ reabsorption (see **Fig. 2**) and augmented by aldosterone secretion owing to volume depletion. Hypokalemia can be severe and occasionally present as muscle paralysis.[98]

Of note, pRTA may also present with inappropriately high urine pH at plasma bicarbonate concentrations above the bicarbonate threshold. The definite diagnosis of dRTA requires demonstration of the acidification defect, which is commonly done indirectly, by calculating the urine anion gap as a surrogate for ammonium measurements in the urine[99–101] (**Box 5**). A negligible or positive urine anion gap in the context of metabolic acidosis is suggestive of dRTA reflecting the absence of ammonium excretion[102] (**Fig. 3**).

The diagnosis of dRTA is relatively straightforward when the child presents with classical clinical and biochemical findings. Incomplete forms of dRTA can pose a diagnostic challenge, because the urine acidification defect is only apparent after a physiologic challenge. Two diagnostic studies have been used to confirm the diagnosis, either loading with ammonium chloride[90,100,102] or the administration of a loop diuretic, for example, furosemide.[102–104] In the first scenario, patients with (incomplete) dRTA will develop metabolic acidosis owing to a lack of proton secretion in the collecting duct (**Fig. 4**). In the second scenario, the loop diuretic will lead to increased distal

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Box 5
Urine anion gap (UAG)

Calculation of the urine anion gap is an indirect method to estimate urinary ammonium (NH_4^+) excretion. UAG is only useful (and valid) for the differential diagnosis of patients with normal anion gap hyperchloremic metabolic acidosis (NAGMA).[1,99–102]
It is determined by subtracting the sum of easily measurable anions from the sum of cations in the urine. The formula resembles the determination of the plasma anion gap.

$$UAG = Na^+ + K^+ - Cl^-$$

Note: In relatively acidic urine (pH < 6.5), the urine bicarbonate concentration (U [HCO_3^-]) is essentially zero and its effect on the UAG is, therefore, negligible.
Unmeasured, and generally negligible are the urine anions sulfate and phosphate and the cations calcium and magnesium. NH_4^+ constitutes the major urine cation, and its excretion is accompanied by chloride as $NH_4^+Cl^-$.
Systemic metabolic acidosis leads physiologically to large urinary ammonium excretion, which serves to trap secreted protons. It is identified by a negative UAG owing to the increased Cl^- excretion that accompanies the unmeasured cation NH_4^+. This scenario is commonly seen in children with severe diarrhea and NAGMA or after acid or NH_4Cl loading.
A small or positive UAG in a patient with NAGMA indicates failure to acidify the urine (see example).
The UAG helps to diagnose patients with proximal renal tubular acidosis when the plasma bicarbonate level is below the bicarbonate threshold. The UAG is negative, because the distal acidification mechanism (proton secretion by type A intercalated cells) is intact.

NH_4^+ excretion and UAG calculation in a study with human volunteers and patients[a]

Group	*Net Acid (μmol/min)*	*U pH*	*U NH_4^+ (mmol/L)*	*U Na^+*	*U K^+*	*U Cl^-*	*UAG*
Healthy controls	26	6.0	14	NA	NA	NA	41
Controls, acid loaded[b]	73	4.9	35	119	86	233	−27
Diarrhea	59	5.6	42	31	25	76	−20
Type 1 renal tubular acidosis	7.2	6.5	7	70	35	79	23
Type 4 renal tubular acidosis	31	6.1	9	64	23	57	30

Urine bicarbonate and protons are in equilibrium with water and CO_2. Urine pH and [HCO_3^-] must be measured in a fresh sample, ideally saved under oil to prevent diffusion of CO_2, which leads to a shift of the equation to the right and an increase in pH.
[a] Extracted from Batlle et al.[100]
[b] Controls received ammonium chloride for 3 days.

Na^+ uptake via ENaC, which creates a favorable gradient for proton secretion by the neighboring type A intercalated cells in the collecting duct (see **Fig. 2**). The procedure has been standardized by the additional administration of a mineralocorticoid, for example, fludrocortisone.[102–104] With both studies, patients with dRTA fail to acidify their urine (see **Fig. 4**).

The differential diagnoses of primary dRTA include acquired disorders, such as autoimmune diseases, idiopathic hypercalciuria, nephrocalcinosis, or nephrotoxic medications (see **Box 1**). Patients with suspected or proven dRTA should undergo audiometry (see **Table 1**).

Proximal (Type 2) Renal Tubular Acidosis

Tubular losses of bicarbonate typically lead to alkaline urine owing to defective (restricted) proximal tubular reabsorption. Distal delivery of nonreabsorbed anion (HCO_3^-) obligates the excretion of Na^+ and K^+, which leads to volume depletion, compensatory aldosterone secretion, and (additional) potassium loss in the urine. However, when the plasma bicarbonate concentration falls below the threshold of tubular

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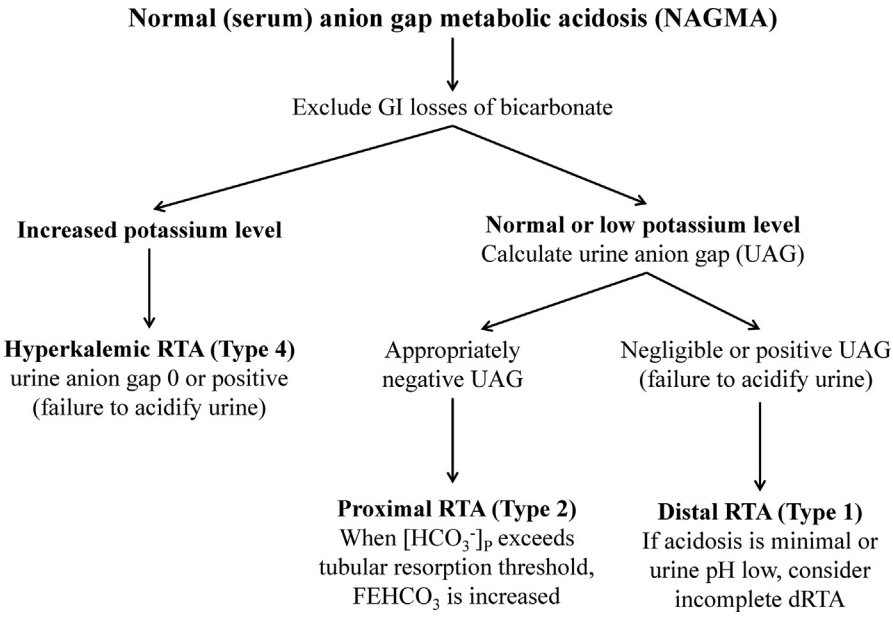

Fig. 3. Algorithm to aid in the differentiation between normal anion gap metabolic acidosis (NAGMA) owing to renal (renal tubular acidosis [RTA]) or extrarenal causes. dRTA, distal renal tubular acidosis; $FEHCO_3$, fractional excretion of bicarbonate; GI, gastrointestinal.

bicarbonate reabsorption, the urine pH decreases to or less than 5.5, because the distal nephron (collecting duct) maintains the ability to acidify the urine. This differentiates pRTA from dRTA. To diagnose pRTA definitively, tubular bicarbonate reabsorption (or fractional excretion of bicarbonate) is assessed at high and low plasma bicarbonate

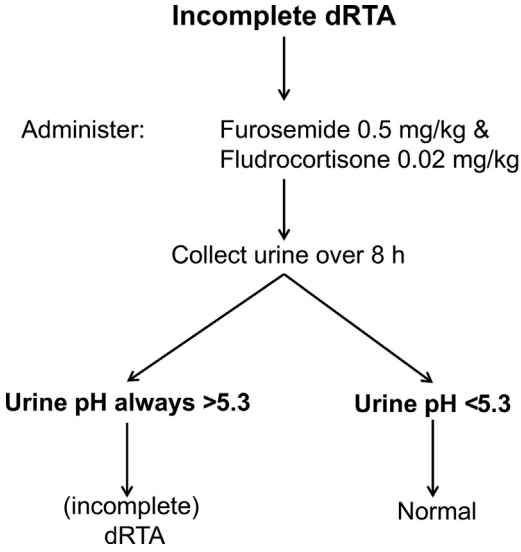

Fig. 4. Diagnostic approach to (suspected) incomplete distal renal tubular acidosis (dRTA). For practical details, see text. (*Adapted from* Alexander RT, Bockenhauer D. Renal tubular acidosis. In: Geary DF, Schaefer F, editors. Pediatric kidney disease. Berlin: Springer; 2016. p. 973–91.)

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concentrations. A fractional excretion greater than 15% (or some authors even suggest >5%)[31,105] in the presence of a metabolic acidosis is diagnostic (**Box 6**).

Tubular bicarbonate excretion can be measured while infusing $NaHCO_3$. Sodium bicarbonate is administered intravenously to increase blood bicarbonate concentrations by 2 mmol/L until urine pH exceeds 5.8. Urine bicarbonate excretion increases at a specific serum bicarbonate concentration, which indicates the bicarbonate threshold[31,106] (see **Box 6**). The physiologic bicarbonate threshold is approximately 22 mmol/L in infants and 25 mmol/L in older children.[106,107] A threshold of less than 20 mmol/L is consistent with pRTA. To rationalize this concept, if the bicarbonate threshold is 16 mmol/L, the patient will stop losing bicarbonate and be able to acidify the urine to less than 5.5 at a plasma HCO_3^- concentration of less than or equal to 16 mmol/L. Detailed protocols for functional testing can be found elsewhere.[102]

MANAGEMENT AND PROGNOSIS OF CHILDREN WITH RENAL TUBULAR ACIDOSIS

Treatment of Children with Distal Renal Tubular Acidosis

Treatment goals are adequate growth and prevention of bony abnormalities, kidney stones, and nephrocalcinosis.[41,59] Hypercalciuria is associated with hypocitruria in patients with dRTA.[108] Alkali therapy is preferably prescribed in the form of potassium or Na/K citrate. Rarely is alkali therapy in excess of 5 mmol/kg/d needed to correct the metabolic acidosis.[41] The ENaC blocker amiloride may be offered to patients with persistent hypokalemia. A comprehensive, interdisciplinary approach is recommended for children with dRTA complicated by hearing loss, hemolytic anemia, or kidney stones.

Treatment of Children with Proximal Renal Tubular Acidosis

The first-line treatment for patients with isolated (genetic) pRTA is supplementation of alkali losses.[109,110] Efforts to increase plasma bicarbonate concentrations are especially relevant in growing children. Depending on the individual bicarbonate threshold, patients may need large quantities of alkali to normalize the blood pH, generally 5 to 15 mmol/kg/d.[59] The amount of bicarbonate required can be decreased by adding a thiazide diuretic.[111] Thiazide-induced inhibition of the apical NaCl cotransporter

Box 6
Fractional excretion of bicarbonate

Calculating the fractional excretion of bicarbonate ($FEHCO_3$) is useful in the differential diagnosis of suspected renal tubular acidosis.

$$FEHCO_3\,(\%) = \frac{[HCO_3]_U \times [Cr]_S}{[HCO_3]_S \times [Cr]_U} \times 100$$

Tubular bicarbonate reabsorption (or conversely, fractional excretion of bicarbonate) is assessed at high and low serum HCO_3^- concentrations.

A $FEHCO_3$ of greater than 15% (or by some authors even >5%) in the presence of metabolic acidosis is diagnostic for proximal renal tubular acidosis.[31,105]

To confirm the diagnosis, serum HCO_3^- is increased to 18 or 20 mmol/L with an intravenous infusion of $NaHCO_3$ at 0.5 to 1 mmol/kg/h. The urine pH (initially expected to be low) will increase to greater than or equal to 7.5 when the threshold for HCO_3 reabsorption is reached. In patients with proximal renal tubular acidosis, the $FEHCO_3$ will exceed 15% or 20% as determined by this formula. Online calculators are available.

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NCC in the distal convoluted tubule results in mild volume depletion, which is thought to increase bicarbonate reabsorption in the loop of Henle and the proximal tubule. Unfortunately, this therapy can worsen preexisting hypokalemia, because it will increase sodium flow to the collecting duct and enhance sodium absorption there, consequently increasing K excretion. K^+ (and alkali) supplementation is preferably given in the form of potassium citrate.[31]

Treatment of Children with Type 4 Renal Tubular Acidosis

Therapeutic management depends on the etiology of the disorder. Underlying kidney diseases should be treated, for example, effective intermittent catherization in children with a dysfunctional bladder. In addition, offending medications should be discontinued. The plasma pH can be corrected with alkali therapy using sodium salts, which may be supplemented with additional NaCl in the presence of sodium wasting. Thiazide diuretics are effective in patients with pseudohypoaldosteronism type 2 (Gordon syndrome).[75,112,113]

Prognosis of Proximal and Distal Renal Tubular Acidosis

Data on the long-term outcome of children with isolated pRTA are limited, owing to the rarity of this disease. Chronic kidney disease and end-stage renal disease have not been reported (in contrast with dRTA). Whereas high-dose alkali therapy and other measures improve plasma pH and growth, normal plasma bicarbonate concentrations are difficult to maintain in pRTA.[114] The prognosis of renal Fanconi syndrome is varied and depends on its etiology. Details can be found elsewhere.[60,115–118]

The prognosis of dRTA, if diagnosed and treated early, is favorable with preserved glomerular filtration rate and improved growth.[119,120] However, delayed diagnosis and persistent acidosis may result in growth impairment, severe bone deformities and, rarely chronic kidney disease.[119,121–124] Alkali therapy does not improve or prevent hearing loss.[125] The outcome of acquired forms of both proximal and dRTA depends on the treatment of the etiology, including the protection from repeated exposure.[126]

SUMMARY

RTA should be suspected in poorly thriving young children with hyperchloremic and hypokalemic (in case of RTA types 1–3) normal anion gap metabolic acidosis, with or without syndromic features. Further workup is needed to determine the type of RTA and the presumed etiopathogenesis (eg, genetic forms, drug-induced, or secondary to autoimmune disorders), which will inform the treatment choices and prognosis. The risk of nephrolithiasis and calcinosis is linked to the presence (pRTA, negligible stone risk) or absence (dRTA, high stone risk) of urine citrate excretion. New formulations of slow-release alkali and potassium combination supplements are currently being tested that are expected to simplify treatment and lead to sustained acidosis correction compared with traditional supplements.

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