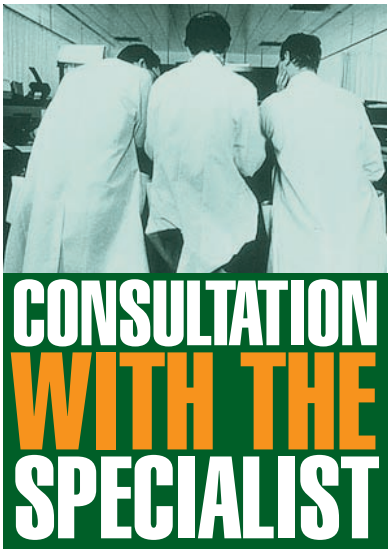

Renal Tubular Acidosis

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Objectives

After completing this article, readers should be able to:

1. Describe the important presenting characteristics of renal tubular acidosis (RTA).
2. Delineate the mechanisms of the growth failure commonly encountered in RTA.
3. Characterize the various types of primary RTA.
4. Describe diagnostic tests and treatment modalities available for RTA.
5. Delineate the conditions giving rise to secondary distal and proximal RTA.

Case Presentation

A 2-month-old Caucasian female presented for failure to thrive. She was born at 33 weeks' gestation via primary cesarean section for pregnancy-induced hypertension to a 38-year-old G1P0 mother. Her birthweight was 1,430 g, making her small for gestational age. Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. Newborn metabolic screen results were negative. At 3 weeks of age, with good oral intake of formula, alternating with breastfeeding, the infant was discharged from the hospital.

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The infant's paternal grandfather died at age 61 from bronchitis and heavy smoking. The 60-year-old paternal grandmother was healthy and well. There was no family member of short stature. The 38-year-old mother (162.6 cm) and the 46-year-old father (175.3 cm) both were in good health. The maternal grandfather, age 72, had a history of renal stones. The 67-year-old maternal grandmother (157.5 cm) had a history of gallstones. No one in the family was on dialysis or had kidney diseases except for the maternal grandfather's renal stones.

At 2 months of age, the infant had persistent failure to thrive and a 1-day history of irritability and vomiting and was readmitted for diagnostic evaluation. Serum bicarbonate level was 12 mEq/L (12 mmol/L), and she was tachypneic, with a respiratory rate of 60 breaths/min and intercostal retraction. Her height was 48.5 cm (<5th percentile) and her weight was 3.45 kg (<5th percentile). Blood pressure was 81/48 mm Hg. She was alert and calm, with normal skin turgor. Chest showed equal expansion and clear breath sounds, with no rales or wheezes. There were distinct heart sounds, a regular rhythm, and no murmur. The abdomen was soft and nontender, had normally active bowel sounds, and had no masses or hepatosplenomegaly. Pulses were full and equal. She had good muscle tone and spontaneous movement of all extremities.

Laboratory values on admission were: blood pH, 7.28; serum sodium, 138 mEq/L (138 mmol/L); potassium, 5.2 mEq/L (5.2 mmol/L); chloride, 113 mEq/L (113 mmol/L); bicarbonate, 12 mEq/L (12 mmol/L); urea nitrogen, 3

mg/dL (1.07 mcmol/L); and creatinine, 0.2 mg/dL (17.7 mcmol/L). Urinalysis showed: pH, 7; specific gravity, 1.003; and no hematuria or albuminuria. Diagnostic evaluation for sepsis was negative, and ceftriaxone was discontinued on the sixth hospital day.

Ultrasonography of the kidneys showed diffuse nephrocalcinosis bilaterally. The right kidney was 5.1 cm and the left kidney 4.8 cm. They appeared normal for age, exhibited normal echogenicity and normal preservation of parenchyma, and had no hydronephrosis or hydroureters.

The alkaline urine pH consistently above 5.5 in the presence of metabolic acidosis and the presence of nephrocalcinosis without a history of diuretic having been used suggested the diagnosis of renal tubular acidosis (RTA).

The urinary calcium-to-creatinine ratio was 0.73 mg. The urinary citrate was 80 mg/g creatinine (normal, >180 mg/g creatinine, Table 1). Urinary oxalate was 1.1 mg/kg per day (normal, <2 mg/kg per day, Table 1).

After intravenous infusion of 4 mEq/kg per day of sodium bicarbonate, the metabolic acidosis was corrected and the tachypnea resolved. The diagnosis of RTA was confirmed when the urine minus blood partial pressure of CO_2 was found to be less than 17 mm Hg initially and 10.7 mm Hg on repeat measurement (normal, >20 mm Hg, Fig. 1). The child was started on Bicitra brand of sodium citrate and citric acid oral solution 5 mL (5 mEq) qid.

During the admission, the infant alternately breastfed and was given 45 mL of iron-fortified forumla (20 kcal/oz) every 3 to 4 hours. On the fourth hospital day, a soy-based formula was substituted. She tolerated Bicitra added to the formula and was discharged from the hospital on the eighth day.

She was evaluated every month for the first 5 months, during which Bicitra (1 mL=1 mEq) was increased to 8 mL tid. At 10 months of age, the dose was adjusted to 12 mL qid and at age 13 months was modified to a daily divided dosage of 12 mL, 12 mL, and 24 mL, with the larger dose at bedtime. The rationale was that growth hormone secretion is highest at night and she would benefit from better correction of metabolic acidosis with a larger dose at bedtime. At 20 months of age, her height was 79 cm (10th percentile) and her weight was 9.23 kg (5th percentile). The average dose of alkali therapy was 5 to 6 mEq/kg per day. She subsequently was followed every 3 months for the third year of life and every 6 months thereafter.

Urine calcium-to-creatinine ratio was monitored at each follow-up visit and was documented at normal values of less than 0.20 mg/mg, usually about 0.08 mg/mg. The bilateral nephrocalcinosis was followed with ultrasonography of the kidneys at 13 months, 20 months, 2 years, 4 years, and 5 years of age. The kidneys continued to grow, but the nephrocalcinosis in the medullary pyramids persisted. At 5 years of age, the right kidney was 7.23 cm and the left kidney 8 cm, which was within normal values. The urine pH was 8 and specific gravity was 1.001, and the urine was negative for blood and protein. The Bicitra therapy was modified at 5 years of age to 24 mL in the morning, 12 mL at noon, and 36 mL at night (total, 5 mEq/kg per day). The corresponding electrolyte pattern was sodium, 139 mEq/L (139 mmol/L); potassium, 4.3 mEq/L (4.3 mmol/L); chloride, 105 mEq/L (105 mmol/L), CO_2, 23 mEq/L (23 mmol/L); serum urea nitrogen, 11 mg/dL (3.9 mmol/L); and creatinine, 0.5 mg/dL (44.2 mcmol/L).

The last ultrasonography was obtained at 6 years of age. Bilateral

Table 1. Normal Indices of Urinary Excretion of Citrate and Other Variables

Index Measurement	Normal Values
Calcium	<4 mg/kg per 24 h Urinary calcium/creatinine ratio: <0.21 mg/mg (adults) <0.41 mg/mg (19 mo to 6 y) <0.60 mg/mg (7 to 18 mo) <0.86 mg/mg (<7 mo)
Oxalate	<50 mg/1.73 m^2 per 24 h (<2 mg/kg per 24 h)
Uric acid	<815 mg/1.73 m^2 per 24 h (35 mg/kg per 24 h)
Cystine	<75 mg/g creatinine
Citrate	>180 mg/g creatinine
Creatinine	Newborns: 8 to 10 mg/kg per 24 h Children: 12 to 10 mg/kg per 24 h Adults: F 12 to 15 mg/kg per 24 h M 15 to 20 mg/kg per 24 h

From Laufer J, Biochis H. Urolithiasis in children: current medical management. *Pediatr Nephrol.* 1989;3:317–331; Sargent JD, Stukel TA, Kresal J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr.* 1993;123:393–397; and Manz F, Kehrt R, Lausen B, Merkel A. Urinary calcium excretion in healthy children and adolescents. *Pediatr Nephrol.* 1999;13:894–899.

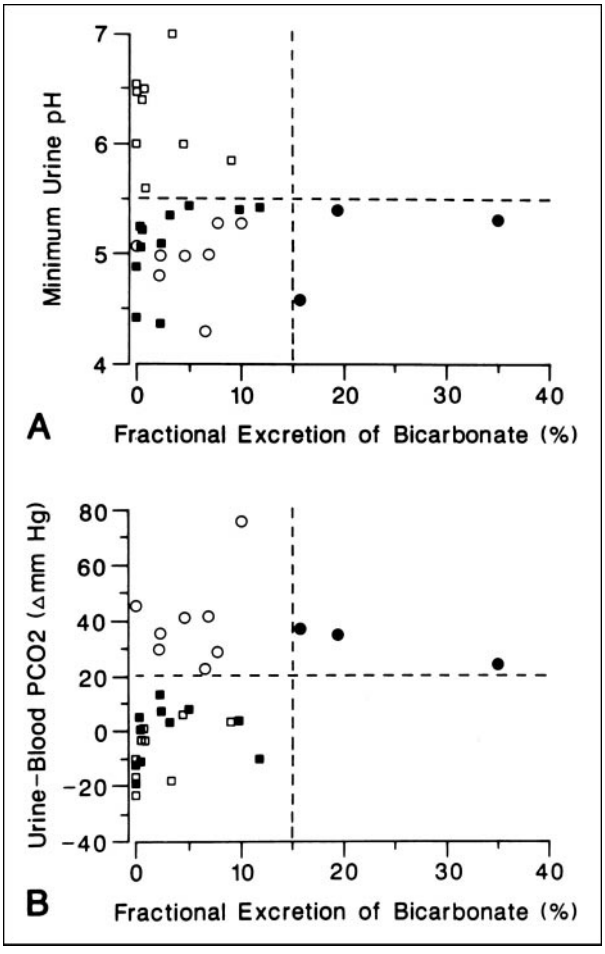

Figure 1. A. Minimum urine pH versus fractional excretion of bicarbonate (%). Closed squares and closed circles represent healthy individuals and patients who have proximal, type 2 RTA, respectively. Open circles represent rate-dependent distal RTA. All three groups have minimum urine pH of less than 5.5. Patients who have classic, type 1 distal RTA, represented by open squares, have minimum urine pH values in excess of 5.5. B. Urine minus blood P_{CO_2} (change in mm Hg) versus fractional excretion of bicarbonate. Healthy individuals (open circles) and patients who have proximal, type 2 RTA (closed circles) have values above 20 mm Hg. In patients who have distal classic, type 1 RTA (open squares) and rate-dependent distal RTA (closed squares), values are less than 20 mm Hg. Reprinted with permission from Strife CF, Clardy CW, Varade WS, Prada AL, Waldo FB. Urine-to-blood carbon dioxide tension gradiant and maximal depression of urinary pH to distinguish rate-dependent from classic distal renal tubular acidosis in children. *J Pediatr.* 1993;122:60–65.

nephrocalcinosis persisted, but the kidney size was normal, with the right kidney at 7.23 cm and the left kidney at 8 cm. The last urinalysis showed a pH of 8.5, specific gravity of 1.000, trace protein, and no blood. The next scheduled follow-up visit is in 9 months.

Case Discussion

The initial growth retardation of the child described in the case is related to the 33-week gestation, but the RTA also plays a significant role. Even with the increased therapeutic dose of Bicitra at 5 mEq/kg per day, growth did not increase significantly until the second year, when a double dose began to be administered before bedtime.

The presence of severe metabolic acidosis with serum bicarbonate less than 12 mEq/L (12 mmol/L) clinically associated with tachypnea illustrates the logical steps to pursue the diagnosis of RTA (Table 2). In many patients, RTA may present with polyuria, constipation, and failure to thrive. The polyuria of RTA is induced partly by the hypercalciuria, but the chronic hypokalemia from potassium wasting (vide infra) also contributes to the lack of urine concentrating ability. Damage to the papillae and their collecting systems caused by interstitial nephritis of chronic hypokalemia also may contribute. The urine specific gravity of this child was consistently low and at the latest follow-up was 1.000. The constipation seen in patients who have RTA is due to the muscle weakness associated with chronic hypokalemia (the gastrointestinal tract is a long muscular tract).

The differential diagnosis of failure to thrive and constipation in infancy must include congenital hypothyroidism (Table 3). Results of thyroid function tests were normal in this child. The classic symptoms of hypothyroidism typically are seen in infancy, especially with screening tests, diagnosis, and treatment in the neonatal period. Today, subclinical hypothyroidism in infancy may present only with failure to thrive. The hyperchloremic metabolic acidosis with normal anion gap documented in this child also could be

Table 2. Diagnostic Evaluation for RTA

Studies	Interpretation
(1) Fresh, spot urine pH	Type 1 RTA, urine pH consistently >5.5. Type 2 RTA, urine pH <5.5.
(2) Serum electrolytes	Metabolic acidosis with serum total CO_2 <17.5 mEq/L (17.5 mmol/L) for all types of RTA, usually associated with hyperchloremia and normal anion gap. Normal serum urea nitrogen, creatinine, and creatinine clearance.
(3) 24-h urine for calcium, citrate, potassium, and oxalate	Hypercalciuria, hypocitraturia, and potassium wasting are associated with type 1 RTA. Rule out hyperoxaluria.
(4) Ultrasonography of the kidneys	Nephrocalcinosis in undiagnosed, untreated, or inadequately treated RTA.
(5) Urine minus blood P_{CO_2}	Normal values, >20 mm Hg Proximal, type 2 RTA, >20 mm Hg Distal, type 1 RTA, <20 mm Hg
(6) Tubular reabsorption of bicarbonate (TRB)	Bicarbonate wasting or TRB >15% in type 2 RTA and <5% in type 1 RTA at normalized serum total CO_2.
(7) Tubular reabsorption of phosphate (TRP)	TRP <60% filtered load of phosphate in Fanconi syndrome and other proximal tubular defects in reabsorption of phosphate. If Fanconi syndrome is suspected, 24-h urine collection is needed to confirm the aminoaciduria and potassium wasting.
(8) Renal acidification studies	If metabolic acidosis is clearly present, with total CO_2 <17.5 mEq/L (17.5 mmol/L), there is no need for further acidification. If the metabolic acidosis is unclear, the renal ability to acidify can be tested maximally after ammonium chloride or arginine hydrochloride acid loading. The net acid excretion of <70 mcEq/min per 1.73m^2 confirms a distal tubular acidification defect.

Steps (1) to (5) are conducted by the generalist. Steps (6) to (8) usually are recommended by the pediatric nephrologist.

Table 3. Differential Diagnosis of Neonatal Failure to Thrive and Normal Anion Gap Metabolic Acidosis

- Distal renal tubular acidosis
- Congenital hypothyroidism
- Obstructive uropathy
- Early uremic acidosis
- Bicarbonate loss
  - —Proximal renal tubular acidosis
  - —Diarrhea
  - —Intestinal fistula
  - —Ureterosigmoidostomy
  - —Medications: cholestyramine, magnesium sulfate, calcium chloride
- Acid loading
  - —Ammonium chloride
  - —Arginine hydrochloride

due to obstructive uropathy. Thus, ultrasonography of the kidneys is appropriate to rule out hydronephrosis and hydroureters of obstructive uropathy. Other causes of metabolic acidosis with normal anion gap (Table 3) include early uremic acidosis, which was unlikely in this child because of the normal serum urea nitrogen and creatinine. The history excluded bicarbonate losses from diarrhea; intestinal fistula; ureterosigmoidostomy; or ingestion of calcium chloride, magnesium sulfate, or cholestyramine. There was no history of acid loading (eg, ammonium chloride or arginine hydrochloride).

After the extracellular bicarbonate and nonbicarbonate buffering systems are exhausted, calcium salts in the skeletal system become the next line of defense against metabolic acidosis. The calcium released in exchange for the hydrogen ion obligates the kidney to increase calcium excretion to maintain calcium homeostasis. Thus, hypercalciuria often accompanies RTA. The hypocitraturia seen in this child, coupled with her high normal urine calcium excretion, increases the risk of nephrocalcinosis, which is characteristic of undiagnosed and untreated RTA. Indeed, if untreated or treated inadequately due to medical noncompliance, the nephrocalcinosis may worsen and ultimately destroy the kidneys, resulting in end-stage renal disease (Fig. 2). However, the nephrocalcinosis in RTA usually is unresolved, even with aggressive alkali therapy, in distinct contrast to diuretic-induced nephrocalcinosis in infancy, which resolves after cessation of the diuretic therapy.

In the past, some research laboratories offered the determination of

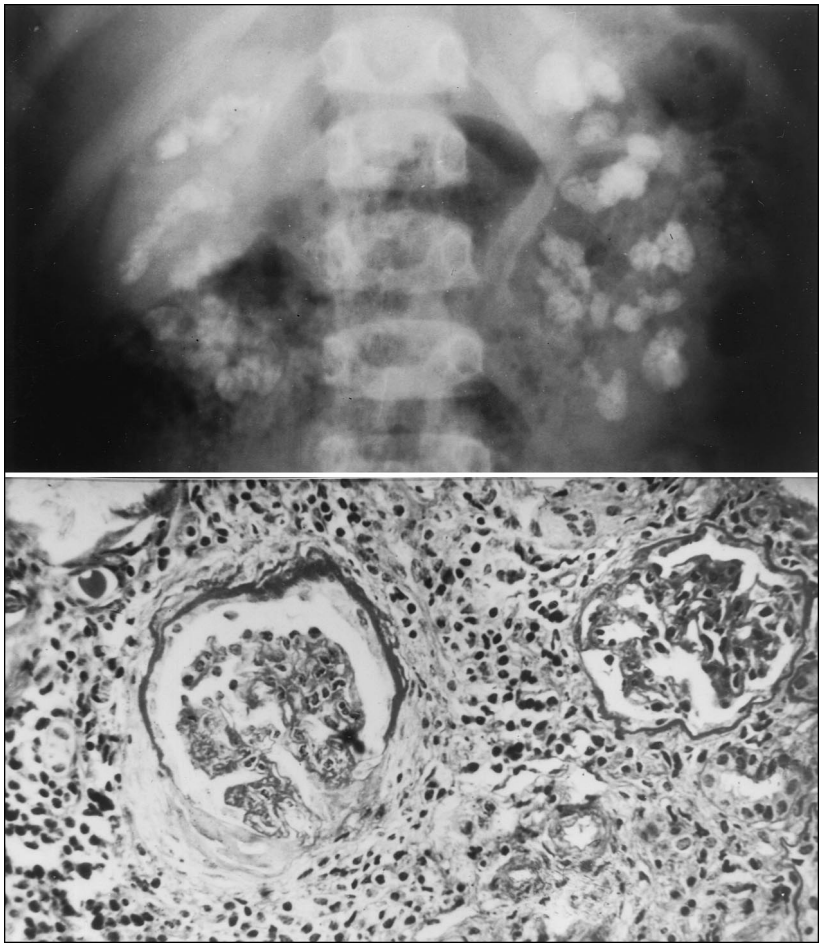

Figure 2. Severe nephrocalcinosis in a 4-year-old child who had unrecognized and untreated RTA and presented from 1 to 4 years of age with failure to thrive and microscopic hematuria before end-stage renal disease. Renal biopsy showed almost complete obliteration of tubules from the massive nephrocalcinosis, glomerulosclerosis, and thickening of the Bowman capsules. Reprinted from Chan JCM. Acid-base, calcium, potassium and aldosterone metabolism in renal tubular acidosis. *Nephron.* 1979;23:153–159. By permission S Karger AG.

urinary pH by glass electrode and urinary net excretion by automatic titrator. These net acid determinations are time-consuming to calibrate and not cost-effective for routine chemistry laboratories. Today, a useful diagnostic confirmation is the urinary minus blood partial pressures of carbon dioxide, as used in this child. For healthy individuals and those who have proximal RTA, the measurement is more than 20 mm Hg (Fig. 1). The value in a child who has distal, type 1 RTA, as seen in this child, is less than 20 mm Hg. This diagnostic test also can be used to confirm the diagnosis of the gradient defect distal RTA. Because blood gas machines are widely available, the partial pressure of CO_2 determination in both urine and blood can be performed easily. A common misconception is that urine is injurious to the blood glass electrodes, but urine does not injure the membrane of the blood gas electrode any more than does blood.

Clinical Findings of RTA

Clinically, RTA is characterized by failure to thrive, polyuria, and constipation. Biochemically, it is characterized by hypokalemic, hyperchloremic metabolic acidosis. The basic defect in type 1 or classic RTA lies in a failure of the distal tubular sodium hydrogen ion exchange, resulting in sodium being wasted by the kidneys in association with bicarbonate wasting. The ensuing contraction of the extracellular volume gives rise to hyperaldosteronism and consequent potassium wasting. The resulting hypokalemia is manifested symptomatically as muscle weakness (including constipation) and lack of renal concentrating ability (polyuria). Occasionally, hyperparathyroidism may be encountered. Osteomalacia in the adult and rickets in the child may be seen. Finally, the hyperchloremic metabolic acidosis gives rise to hypercalciuria and hypocitraturia, leading to nephrocalcinosis and nephrolithiasis as a complication of unrecognized and untreated RTA. The hypercalciuria further contributes to the polyuria. Chronic metabolic acidosis obligates the skeletal buffering of the extra hydrogen ion. In addition, acidosis stimulates mitochondrial citrate oxidation, resulting in a reduction in the renal excretion of citrate, which is a physiologic calcium chelater that acts to increase calcium solubility. Thus, the hypercalciuria coupled with hypocitraturia make supersaturation probable and nephrocalcinosis likely.

The urine calcium-to-creatinine ratio of 0.73 mg/mg reported for the child in the case was on the high side of normal for a 2-month-old (Table 1). The nephrocalcinosis was

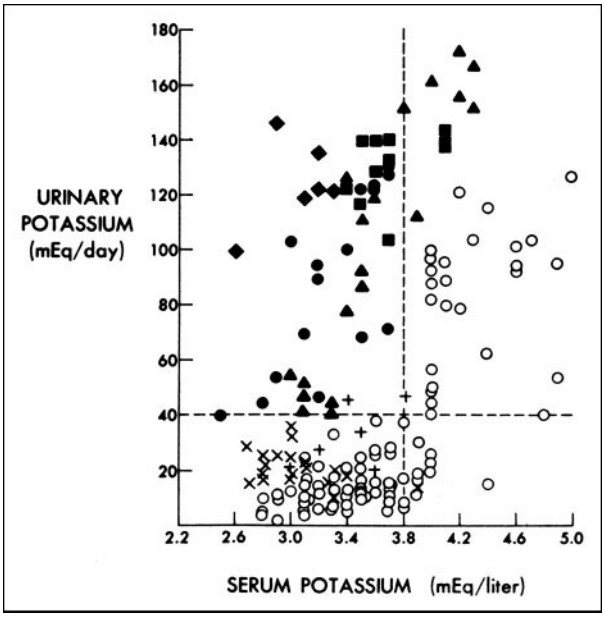

Figure 3. Potassium wasting in patients who have RTA (closed pyramids, circles, and squares) versus potassium excretion in healthy individuals from different publications (open circles and crosses). Reprinted from Sebastian A, McSherry E, Morris RC Jr. Renal potassium wasting in renal tubular acidosis (RTA). *J Clin Invest.* 1971;50:667–678. By permission Society of Clinical Investigation.

already present, and there is a possibility that even more severe hypercalciuria and hypocitraturia already was present. The earliest case of nephrocalcinosis in RTA was seen in a 3-week-old infant who had distal RTA. Nephrocalcinosis is encountered more frequently in type 1 RTA and uncommonly in type 2 RTA. The retention of hydrogen ion in type 1 RTA obligates the hypercalciuria and increases the risk of nephrocalcinosis. In contrast, type 2 RTA is more difficult to treat because of the frequent and massive doses of Bicitra needed to counteract the massive bicarbonate wastings.

Type 1 Distal RTA

Type 1 RTA (also known as classic RTA) is characterized by hyperchloremic metabolic acidosis and hypokalemia. The urinary pH is always in excess of 5.5, with net acid excretion of less than 70 mcEq/min per 1.73 m^2. When metabolic acidosis is corrected by base therapy, less than 3% of the filtered load of bicarbonate is excreted in the final urine output.

The severe potassium wasting of RTA is illustrated in Figure 3. When healthy individuals sustain hypokalemia of less than 3.8 mEq/L (3.8 mmol/L), the kidneys respond by conserving potassium, and urinary potassium excretion falls below 40 mEq/d. However, in patients who have distal RTA, the degree of potassium wasting continues irrespective of the severity of hypokalemia. This remarkable potassium wasting is believed to be a reflection of the hyperaldosteronism associated with the volume contraction in type 1, distal RTA. The conditions that may cause secondary distal RTA are listed in Table 4.

Type 2, Proximal RTA

Type 2 RTA is characterized by bicarbonate wasting with a resetting of the threshold for proximal tubular bicarbonate reabsorption. Instead of the normal bicarbonate reabsorption threshold of 26 mEq/L (26 mmol/L), it is reset to a much lower rate in type 2 RTA. For example, if the bicarbonate reabsorption threshold is set at 15 mEq/L (15 mmol/L), bicarbonate wasting begins when this threshold is exceeded and, thus, the plasma bicarbonate is set correspondingly at 15 mEq/L (15 mmol/L). One of the best schematic presentations of urine bicarbonate leakage in proximal RTA is illustrated in Figure 4. In normal subjects, whose plasma bicarbonate concentrations are 26 mEq/L (26 mmol/L), 85% of the filtered load of bicarbonate is reabsorbed in the proximal tubules and 15% in the distal tubule in exchange with hydrogen ions. This leaves no bicarbonate in the final urine, and the acidic urine pH of 5.5 is maintained. Patients who have proximal type 2 RTA, however, have a lower-than-normal set point for bicarbonate reabsorption threshold (eg, at a serum bicarbonate of 15 mEq/l [15 mmol/L]). In this case, the proximal tubular reabsorption of bicarbonate at 60% coupled with the distal tubule of bicarbonate reabsorption of 15% is still sufficient to absorb all the filtered load of bicarbonate, and the urinary pH remains at 5.5. However, with progressive bicarbonate correction of the serum bicarbonate to normal concentrations, the 60% proximal tubular bicarbonate reabsorption and 15% distal reabsorption is insufficient to reabsorb all the filtered load of

Table 4. Clinical Spectrum of Secondary Type 1, Distal RTA

- *Tubulointerstitial renal disorders*
  - —Obstructive uropathy
  - —Medullary sponge kidney
  - —Renal transplantation
  - —Nephrocalcinosis induced by metabolic and endocrine disorders
    - Vitamin D intoxication
    - Hyperparathyroidism
    - Idiopathic hypercalicuria
    - Wilson disease
    - Hyperthyroidism
- *Genetically transmitted systemic diseases*
  - —Ehlers-Danlos syndrome
  - —Marfan syndrome
  - —Osteopetrosis with associated nerve deafness
  - —Sickle cell anemia
  - —Elliptocytosis
  - —Carbonic anhydrase deficiency
  - —Hereditary fructose intolerance
  - —Fabry disease
- *Autoimmune disease*
  - —Sjögren syndrome
  - —Hypergammaglobulinemic disorders
  - —Systemic lupus erythematosus
  - —Chronic active hepatitis
  - —Thyroiditis
- *Toxin- or drug-induced*
  - —Amphotericin B
  - —Lithium
  - —Analgesics
  - —Cyclamate
  - —Toluene
- *Hyponatriuric states*
  - —Nephrotic syndrome
  - —Hepatic cirrhosis

From Hanna JD, Santos F, Chan JCM. Renal tubular acidosis. In: *Clinical Pediatric Nephrology*. New York, NY: McGraw-Hill, Inc; 1992:665–698.

bicarbonate, resulting in an alkaline urine pH of 7.8.

The conditions that may cause secondary proximal RTA are listed in Table 5.

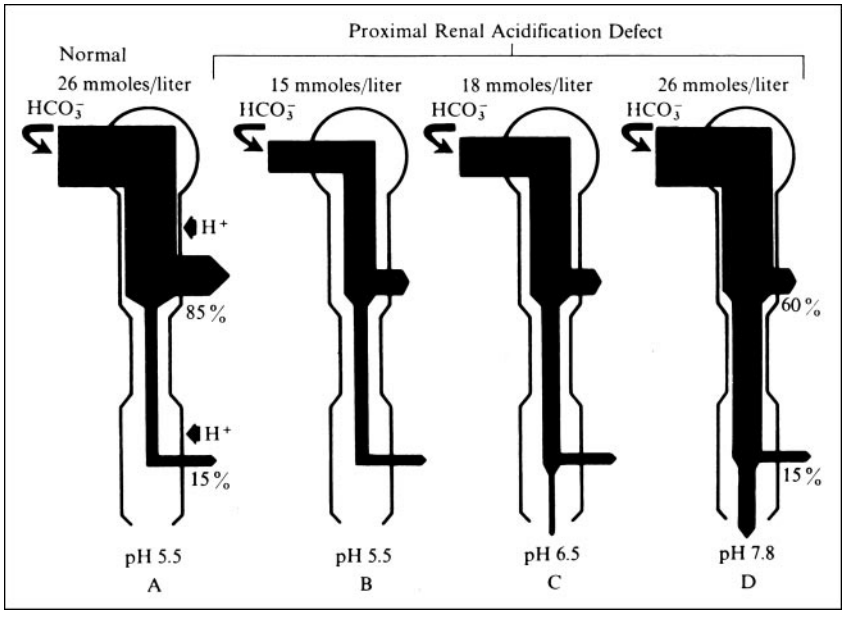

Figure 4. Nephron in a normal individual (diagram to left) showing plasma bicarbonate of 26 mEq/L (26 mmol/L) and reabsorption of the filtered load of bicarbonate in the proximal tubules (85%) and in the distal tubule (15%). In contrast is the acidotic patient who has proximal, type 2 RTA with a plasma bicarbonate of 15 mEq/L (15 mmol/L) (diagram to extreme right) and after correction of metabolic acidosis with bicarbonate therapy. The filtered load of bicarbonate exceeds the proximal tubule's ability to absorb bicarbonate (only at 60%) and at the distal tubule (15%). With correction of acidosis, the massive bicarbonate leak causes an alkaline urine pH of 7.8. From Morris RC, Sebastian A, McSherry E. Renal acidosis. *Kidney Int.* 1972;1:322–340. By permission International Society of Nephrology.

Type 3 RTA

Infants who have mild, distal renal tubular acidification defect combined with mild proximal bicarbonate reabsorption defect were classified previously as having type 3 RTA. This has been reclassified as a subtype of type 1 RTA that occurs primarily in preterm infants.

Type 4 RTA

Type 4 RTA is due to either aldosterone deficiency or aldosterone resistance that results in an inability to excrete hydrogen and potassium ions. Retention of these ions gives rise to systemic metabolic acidosis and hyperkalemia. The latter features distinguish type 4 RTA from the hypokalemia, which commonly characterizes the first two types of RTA. Aldosterone deficiency may result from congenital adrenogenital syndrome, and aldosterone resistance may follow relief of posterior urethral valve obstruction or prostatic hypertrophy.

The More Common Type

Previously, type 1 RTA was considered the most common type of RTA followed by type 4 RTA, but with more awareness of type 4 RTA following obstructive uropathy, it now is regarded as the most common type. Elderly men who have obstructive uropathy from prostatic hypertrophy and infants who have congenital adrenogenital syndrome give rise to more type 4 RTA than all the other types.

Table 5. Clinical Spectrum of Type 2, Proximal RTA

- *Isolated RTA*
  - —Primary (sporadic or familial)
  - —Carbonic anhydrase inhibition
    - Acetazolamide
    - Mafenide (sulfamylon)
    - Carbonic anhydrase deficiency
    - Osteopetrosis with carbonic anhydrase II deficiency
- *Generalized*
  - —Primary (sporadic or familial)
  - —Inborn error of metabolism
    - Cystinosis
    - Lowe syndrome
    - Hereditary fructose intolerance
    - Tyrosinemia
    - Galactosemia
    - Wilson disease
    - Pyruvate carboxylase deficiency
    - Metachromatic leukodystrophy
    - Glycogen storage disease
  - —Dysproteinemic states
    - Multiple myeloma
    - Light chain disease
    - Monoclonal gammopathy
    - Amyloidosis
  - —Vitamin D deficiency, dependence, or resistance
  - —Interstitial renal disease
    - Sjögren syndrome
    - Medullary cystic disease
    - Renal transplantation rejection (early)
    - Balkan nephropathy
    - Chronic renal vein thrombosis
  - —Toxins
    - Outdated tetracyclines
    - Lead
    - Mercury
    - Gentamicin
    - Cadmium
    - Maleic acid
    - Coumarin
    - Streptozocin
  - —Miscellaneous
    - Nephrotic syndrome
    - Paroxysmal nocturnal hemoglobinuria
    - Malignancy
    - Congenital heart disease

From Hanna JD, Santos F, Chan JCM. Renal tubular acidosis. In: *Clinical Pediatric Nephrology*. New York, NY: McGraw-Hill, Inc; 1992:665–698.

Rate-dependent Distal RTA

For children, type 1 RTA is difficult to differentiate clinically from rate-dependent distal RTA. The age of presentation, the incidence of failure to thrive, coexisting disorders, and the incidence of nephrocalcinosis are indistinguishable between the two types. The confounding variable is the ability of rate-dependent distal RTA to elaborate the minimum urine pH of less than 5.5. Thus, using the minimum urinary pH, the rate-dependent distal RTA may be misdiagnosed. The ability to arrive at the correct diagnosis of rate-dependent distal RTA requires calculation of the urine minus blood partial pressure CO_2.

Mechanism of Growth Failure

In an abstract presented in 1979, McSherry reported the blunting of growth hormone release in children who have RTA (see Suggested Reading). To determine how metabolic acidosis affects growth hormone secretion and expression, Challa and associates recently demonstrated that acidosis inhibits the growth hormone pulse amplitude, pulse area, and total growth hormone secretion in acidotic animals compared with that of control and pair-fed animals (see Suggested Reading). They also demonstrated that serum insulin-like growth factor (IGF), hepatic IGF-1 mRNA, hepatic growth hormone receptor mRNA, and gene expression of IGF at the growth plate of the long bone all are suppressed in the presence of metabolic acidosis. Thus, it appears that acidosis interferes with major aspects of the growth hormone-IGF axis, although reduced nutrition from acidosis-induced anorexia may contribute to decreased growth hormone secretion. However, metabolic acidosis appeared to inhibit IGF-1 mRNA expression in the growth plate of the long bone and in the hepatic growth hormone receptor mRNA specifically. These animal experiments showed that metabolic acidosis directly inhibited growth hormone secretion and gene expression at target sites, anomalies that contribute to the growth failure of metabolic acidosis.

Data from the 1950s and 1960s

showed impaired intestinal calcium absorption in young children who had RTA. The pathogenesis of this lack of absorption was not elucidated. Studies of acidotic animals in the 1970s showed that ammonium chloride-induced metabolic acidosis interfered with 1-alpha-hydroxylase activation of the vitamin D system. By inference, the impaired absorption of calcium in children who have RTA is likely the result of interference with 1-alpha-hydroxylase activity in the presence of metabolic acidosis. However, data from Chesney and associates (see Suggested Reading) showed no abnormalities in serum 1,25-dihydroxyvitamin D concentrations among children who had RTA, although the serum bicarbonate concentrations of 18 mEq/L (18 mmol/L) suggested that the acidosis was mild and may account for the lack of interference of 1-alpha-hydroxylase activity.

Diagnostic Evaluation

If RTA is suspected, the diagnostic evaluation delineated in Table 2 should be followed. The fresh early morning urine pH should be tested by dipstick. Although a urine pH determined by the glass electrode is more accurate, this is available only at specialized laboratories. An alkaline urine pH in excess of 5.5 in the presence of systemic metabolic acidosis (serum bicarbonate <17.5 mEq/L [17.5 mmol/L] and blood pH <7.4) is suggestive of type 1 RTA.

Because of the association with hypercalciuria in the presence of metabolic acidosis, the urinary calcium-to-creatinine excretion ratio should be obtained. Normal values are less than 0.21 (mg/mg). A notable exception to this value is seen in the first few years of life (Table 1), with the smaller body muscle mass resulting in a lower urine creatinine value. With a smaller denominator, the ratio is higher. However, such "normal" values for infants have been confirmed by the total 24-hour calcium excretion.

Urinary citrate has been shown to be lowered significantly in RTA and is one of the contributing factors to the nephrocalcinosis. Normal urine citrate excretion is in excess of 180 mg/g of creatinine. Other useful indices of urinary excretion are summarized in Table 1.

Ultrasonography of the kidneys can evaluate their anatomic size and echogenicity; rule out dysplastic kidneys, obstructive uropathies, and cystic kidneys; and detect nephrocalcinosis. Any nephrocalcinosis should be monitored by ultrasonography at intervals of every 12 months and if stable, every 2 to 3 years.

When metabolic acidosis is corrected with sufficient alkali therapy, the urine minus blood partial pressure of CO_2 can help differentiate distal from proximal RTA (Table 2).

At this point, the generalist will have completed all appropriate evaluations. The next step is referral to the pediatric nephrologist for determination of tubular reabsorption of bicarbonate and phosphate or renal acidification tests (Table 2).

Treatment

The treatment of type 1 and type 2 RTA is relatively simple, requiring the use of sodium bicarbonate or the slightly more palatable compound Shohl solution (or Bicitra), which contains citric acid and sodium citrate, providing 1 mEq/mL of alkali. Polycitra K solutions contain potassium citrate to provide 2 mEq/mL of alkali and 2 mEq/mL of potassium, designed to correct both the acidosis and hypokalemia.

Santos et al studied the dosage of alkali therapy to maintain a stabilized correction of metabolic acidosis in infants and children who had type 1, distal RTA (see Suggested Reading). Their data suggested that a mean dose of 3.5 mEq/kg per day was needed. They also demonstrated a very large spectrum of therapeutic ranges for alkali therapy from 1 to 7 mEq/kg per day. There was no difference in dose requirements between infants and children on a body weight basis. Their data also suggested a significant increase in percentile weight and height in many treated children. Nonetheless, the large spectrum of variability likely reflects medical noncompliance. Type 2 RTA requires larger and more frequent doses of Bicitra (as high as 14 mEq/kg per day).

Type 4 RTA may require treatment with fludrocortisone 0.1 to 0.3 mg/d (0.05 to 0.15 mg/m^2 per day). To reverse the hyperkalemia that characterizes the metabolic acidosis of type 4 RTA, dietary potassium restriction and orally administered potassium binders may be needed. Finally, to increase renal excretion of potassium, chlorothiazide and furosemide may be required to correct hyperkalemia. To neutralize the metabolic acidosis, bicarbonate therapy of 1.5 to 2.0 mEq/kg per day has been advocated.

Long-term Follow-up of RTA

The effects of therapy should be monitored (Table 6) every month for the first 6 months. Close monitoring of serum bicarbonate concentration, urinary calcium/creatinine ratio, and linear growth allow better adjustments of medication to maintain serum bicarbonate to more than 22 mEq/L (22 mmol/L) and to reverse hypercalciuria. Annual ultrasonographic imaging of the kidneys is used to monitor the nephrocalcinosis. In type 1 RTA, the base needed to neutralize the endogenous hydrogen ion production is much less than in type 2 RTA, where there

Table 6. **Follow-up of RTA**

Studies	Interpretation
Serum total CO_2	Adequate base therapy to maintain serum total CO_2 >22 mEq/L (22 mmol/L).
Spot urine calcium/creatinine ratio	Adequate base therapy to maintain urine calcium/creatinine ratio to <0.20 mg/mg.
Ultrasonography of the kidneys	Monitor nephrocalcinosis.

is massive bicarbonate wasting. Accordingly, type 1 RTA is easier to treat because of the lower alkali requirement (Bicitra 3 to 4 mEq/kg per day) to maintain acid-base equilibrium. The large bicarbonate wasting of type 2 RTA may require up to 14 mEq/kg per day. The larger dose and frequency of dosing makes compliance a problem.

We advocate a larger dose of Bicitra at bedtime for type 1 RTA based on the rationale that growth hormone secretion is maximal during sleep and that the optimal correction of metabolic acidosis during this period will have a significant beneficial effect. Probably all types of RTA can benefit from this strategy, not only in terms of better growth, but to achieve a degree of compliance once or twice a day.

One long-term follow-up of 28 primary type 1, distal RTA patients showed that those who had rickets at the time of presentation responded poorly to therapy, with inferior growth compared with those who did not have rickets. Earlier studies indicated a variable rate of response to therapy, with accelerated growth in some after a few months of therapy and others requiring 1 or more years of therapy before achieving 3rd percentile linear growth curve. Further, the threshold for bicarbonate reabsorption matured with age in type 2, proximal RTA, and in some index patients, this reverted to normal by 8 years of age. Bicarbonate therapy can be discontinued when metabolic acidosis resolves. No data are available on the long-term outcome of type 4 RTA because the prognosis is so variable and entirely dependent on the underlying causes.

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PIR Quiz

Quiz also available online at *www.pedsinreview.org.*

11. A 9-month-old boy presents with a 2-day history of vomiting and diarrhea. The mother states that the boy has had 8 to 10 loose stools per day and has been vomiting most of his feedings. Physical examination shows a dehydrated child who has a rectal temperature of 98°F (36.6°C), respirations of 28 breaths/min, heart rate of 140 beats/min, and blood pressure of 86/58 mm Hg. Mucous membranes and conjunctivae are dry. Skin turgor is diminished, and capillary refill time is 3 seconds. Laboratory examination shows serum sodium, 132 mEq/L (132 mmol/L); potassium, 4.2 mEq/L (4.2 mmol/L); chloride, 104 mEq/L (104 mmol/L); and bicarbonate, 12 mEq/L (12 mmol/L). Capillary blood gas shows a pH of 7.18 and P_{CO_2} of 24 torr. Urine volume is 0.5 mL/kg per hour, and urine pH is 4.5. Which one of the following *best* explains his acidosis?

    A. Accumulation of organic acids.
    B. Aldosterone deficiency.
    C. Bicarbonate loss in the distal tubule.
    D. Bicarbonate loss in the gastrointestinal tract.
    E. Bicarbonate loss in the proximal tubule.

12. A 10-month-old girl presents with poor feeding, constipation, irritability, and failure to gain weight. Physical examination reveals length at the 10th percentile, weight below the 3rd percentile, respirations of 26 breaths/min, heart rate of 98 beats/min, and blood pressure of 86/54 mm Hg. Muscle mass and subcutaneous fat are diminished. Laboratory findings include serum sodium, 134 mEq/L (134 mmol/L); potassium, 3.1 mEq/L (3.1 mmol/L); chloride, 110 mEq/L (110 mmol/L); and bicarbonate, 12 mEq/L (12 mmol/L). Blood urea nitrogen is 4 mg/dL (1.43 mmol/L) and serum creatinine is 0.2 mg/dL (17.7 mcmol/L). Capillary blood gas shows a pH of 7.18 and P_{CO_2} of 24 torr. Urine pH is 7, P_{CO_2} is 5 torr, and specific gravity is 1.004. Renal ultrasonography shows bilateral nephrocalcinosis. Which of the following is the *most* likely diagnosis?

    A. Organic acidemia.
    B. Type 1 renal tubular acidosis.
    C. Type 2 renal tubular acidosis.
    D. Type 3 renal tubular acidosis.
    E. Type 4 renal tubular acidosis.

13. An 11-month-old boy presents with poor weight gain. He was born at term via a normal vaginal delivery. Physical examination reveals weight below the 3rd percentile and length at the 10th percentile. There is poor subcutaneous fat over the abdomen and thighs. Urinalysis shows a pH of 6.0 and specific gravity of 1008. Capillary blood gas reveals pH of 7.28, P_{CO_2} of 28 torr, and bicarbonate of 14 mEq/L (14 mmol/L). Which of the following findings is *most* consistent with the diagnosis of proximal renal tubular acidosis?

    A. Hyperkalemia.
    B. Inability to acidify urine pH below 5.5.
    C. Lack of renal concentrating ability.
    D. Nephrocalcinosis.
    E. Urine − blood P_{CO_2} gradient above 20 mm Hg.

14. Which of the following statements regarding distal renal tubular acidosis is *true*?

    A. Net renal hydrogen ion excretion is decreased.
    B. Renal bicarbonate reabsorption is completed at a lower level.
    C. Renal tubules are less responsive to aldosterone.
    D. Serum anion gap is increased.
    E. Urinary pH below 5.5 can be achieved when serum bicarbonate decreases.