

# Renal tubular acidosis in childhood

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Increased knowledge on the genetics, the pathophysiology, the natural history and the treatment of renal tubular acidosis (RTA) has begun to clarify this often confusing field. To help pediatricians better acquainted with the physiological and genetic basis of the various types of RTA, to facilitate early diagnosis and treatment with the ultimate aim of preventing the significant growth failure and chronic kidney failure of undiagnosed and untreated patients with RTA, we reviewed new data on the mechanisms of growth retardation in patients with RTA. RTA should be included in the differential diagnosis of a child with growth failure, rickets and metabolic acidosis. The diagnostic work-up and treatment are succinctly presented in this review.

*World J Pediatr* 2007;3(2):92-97

**Key words:** renal tubular acidosis; growth retardation; chronic kidney failure; nephrocalcinosis; nephrolithiasis

types of RTA were considered primary types of RTA. Subsequently, many secondary forms of both type 1 and type 2 RTA have been recognized. These major types of RTA, together with descriptions of type 4 RTA will be the subject of this review.

## Net acid balance and why hypercalciuria and nephrocalcinosis occur more commonly in type 1 RTA and uncommonly in type 2 RTA

In a normal individual, hydrogen ions produced daily from endogenous metabolism amount to net acid production of 1 mEq/kg body weight in adults, 2 mEq/kg body weight in children and slightly higher in infants.<sup>[5,6]</sup> To maintain balance, the same amounts of hydrogen ions are excreted by the kidneys as titratable acid plus ammonium.<sup>[5-7]</sup>

Urinary net acid excretion is the sum of titratable acidity plus ammonium minus trace bicarbonaturia.<sup>[7]</sup> In type 1 RTA, the renal acidification defect at the distal renal tubule results in a significant reduction in net acid excretion.<sup>[5]</sup> With endogenous production of net acid proceeding at the usual rate, this reduced net acid excretion in type 1 RTA results in positive hydrogen ion balance.<sup>[6]</sup> Against this positive hydrogen ion balance, the patient's first line of defense against acidosis lies in the intracellular and extracellular bicarbonate and non-bicarbonate buffering systems.<sup>[5-7]</sup> The second line of defense relies on renal excretion of net acid. The third line of defense comes into play with chronic acidosis and relies on skeletal buffering.<sup>[5,6]</sup> This hydroxyapatite buffering of hydrogen ions gives rise to skeletal calcium loss and hypercalciuria.<sup>[6]</sup> In light of the still poorly understood hypocitraturia,<sup>[8]</sup> which characterizes RTA patients, calcium solubility in the RTA patients' urine is significantly lowered. The hypocitraturia coupled with hypercalciuria and alkaline urine pH in RTA patients increases the risk of nephrocalcinosis and nephrolithiasis, which characterize undiagnosed and untreated type 1 RTA.<sup>[9,10]</sup>

In contrast, in type 2 RTA, there is no acidification defect at the distal renal tubule because the defect lies in the proximal tubular inability to reabsorb the filtered load of bicarbonate.<sup>[5,6]</sup> Thus, there is clinical metabolic acidosis because of the lowered tubular

## Introduction

Although osteomalacia and rickets were described in the late 1940s as features of renal tubular acidosis (RTA),<sup>[1]</sup> the characteristic renal acidification defect in infants was not described until the early 1950s.<sup>[2,3]</sup> These were the first descriptions of distal (or classic, type 1) RTA. In the 1960s, Rodriguez-Soriano et al<sup>[4]</sup> delineated another type of RTA from a proximal renal tubular defect, which was characterized by large amounts of urinary bicarbonate wasting. This became known as proximal (type 2) RTA. These two

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threshold of bicarbonate reabsorption, but no net acid retention. The urinary citrate excretion in type 2 RTA is normal or elevated due to decreased proximal tubular reabsorption of citrate. These characteristics coupled with the lack of positive net acid balance in type 2 RTA account for the infrequency in nephrocalcinosis and nephrolithiasis in type 2, proximal RTA.<sup>[9,10]</sup>

### Enigma on the growth retardation in RTA

The stunted growth, common in infants and children with undiagnosed RTA, could not be explained simply on the basis of rickets, as first described in RTA by Albright et al,<sup>[1]</sup> Doxiadis et al<sup>[2]</sup> and Lightwood et al.<sup>[3]</sup>

In an abstract presented in 1979, McSherry et al<sup>[11]</sup> reported the blunting of growth hormone release in children with RTA. But such a mechanism for the growth failure of persistent acidosis remained challenging owing to lack of data on the pulsatile secretion, pulse amplitude, gene expression of growth hormone or insulin-like growth factor (IGF), until a series of animal experiments from the laboratory of Chan and Krieg in the 1990s.<sup>[12-14]</sup> The experimental data of Challa et al<sup>[12,13]</sup> provided the evidence how metabolic acidosis affects growth hormone secretion and expression. The growth hormone pulse amplitude, pulse area, and total growth hormone secretion were inhibited in acidotic animals compared with those in control and pair-fed animals. These investigators also demonstrated that serum IGF, hepatic IGF-1 mRNA, hepatic growth hormone receptor mRNA, and gene expression of IGF at the growth plate of the long bone are all suppressed in the presence of metabolic acidosis. Thus, it appears that the enigma of how acidosis causes growth failure can now be attributed to acidosis-induced interference at the major sites of the growth/IGF axis, although reduced nutrition from acidosis-induced anorexia may also contribute to decreased growth hormone secretion.<sup>[12,13]</sup> To summarize, these animal experiments by Challa et al<sup>[12,13]</sup> and Hanna et al<sup>[14]</sup> have shown that metabolic acidosis directly inhibited growth hormone secretion and gene expression at target sites, anomalies that contribute to the growth failure of metabolic acidosis.

Finally, Carbajo et al<sup>[15]</sup> demonstrated marked changes in the morphology and dynamics of long bone growth cartilage in young rats with sustained metabolic acidosis.

### Physiological basis of various types of RTA

The primary defect of RTA is a renal tubular acidification dysfunction unrelated to any reduction in glomerular filtration rate.<sup>[6,9]</sup> Without azotemia, the serum anion gap  $[\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)]$  is normal in classic RTA, obligating chloride reabsorption to maintain serum electrolyte balance, hence hyperchloremia often accompanies the normal serum anion gap metabolic acidosis.

Three main forms of RTA exist. They can be differentiated on physiological concepts, based on which segment of the renal tubule is affected. Both primary and secondary types exist together with inherited RTA disorders.<sup>[6,9]</sup>

Primary type 1 RTA is due to an isolated acidification defect in the distal renal tubule, which may be sporadic or familial. Secondary type 1 RTA is secondary to a host of conditions, including obstructive uropathy, medullary sponge kidney, sickle cell anemia, Sjögren's syndrome and other autoimmune diseases, amphotericin B and other drug-induced toxicity.<sup>[9]</sup>

Primary type 2 RTA is due to an isolated defect in proximal tubular reabsorption of the filtered load of bicarbonate.<sup>[9]</sup> Secondary type 2 RTA is secondary to a host of conditions, including cystinosis, Lowe's syndrome and other inborn errors of metabolism, multiple myeloma and other dysproteinemic states, vitamin D deficiency, dependence or resistance. Finally, secondary type 2 RTA may arise secondary to toxins such as lead, mercury, gentamicin and cadmium,<sup>[9]</sup> resulting in toxic injury to the proximal renal tubule.

Type 3 RTA is not a pathologic form but a renal tubular maturation delay, primarily seen in premature infants.<sup>[6,9]</sup> Therefore it is no longer regarded as a separate type of RTA and has been reclassified as a subtype of type 1 RTA often presenting in preterm infants with a mixed distal acidification defect combined with mild bicarbonaturia due to immaturity of proximal tubular bicarbonate reabsorption. This transient defect resolves as the infant grows and matures.<sup>[6,9]</sup>

Type 4 RTA is secondary to aldosterone deficiency or aldosterone resistance. These conditions result in an inability to excrete hydrogen and potassium ions.<sup>[9,10]</sup> The most common cause of aldosterone deficiency in infancy is congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency.<sup>[6,9]</sup> In adults, the most common cause is prostate hypertrophy related obstructive uropathy. Indeed, in the 1980s type 4 RTA was first described following release of urinary tract obstruction from prostate hypertrophy in elderly men.<sup>[16]</sup> In view of the fact that these conditions are more common than primary type 1 or type 2 RTA, type 4 RTA is the most commonly encountered RTA.

### Genetic basis of various types of RTA

Congenital defects in the genes regulating the several transport systems involved in the tubular control of acid-base equilibrium lead to the different types of primary RTA. The kidneys reabsorb the filtered bicarbonate and, in addition, reconstitute the bicarbonate used in buffering the fixed acid produced daily. The bulk of bicarbonate reabsorption takes place in the proximal tubule whereas the excretion of hydrogen ions with the coupled recovery of bicarbonate

occurs in the distal nephron.

Bicarbonate is reabsorbed in the proximal tubule by a  $\text{Na}^+\text{-H}^+$  exchanger (NHE3) located at the luminal membrane and a  $\text{Na}^+\text{-HCO}_3^-$  cotransporter (NBC1) located at the basolateral membrane. The  $\text{H}^+$  secreted to the tubular lumen in exchange with  $\text{Na}^+$  as well as the  $\text{HCO}_3^-$  cotransported with  $\text{Na}^+$  at the basolateral membrane result from the ionization of carbonic acid which is formed inside the cell by the hydration of  $\text{CO}_2$ , a reaction catalyzed by a soluble cytoplasmic carbonic anhydrase (CA II). In the tubular lumen, the secreted  $\text{H}^+$  reacts with filtered bicarbonate to form  $\text{H}_2\text{CO}_3$  which is quickly dissociated into  $\text{CO}_2$  and  $\text{H}_2\text{O}$  by the action of other carbonic anhydrase (CA IV) located in the luminal side of the tubular membrane. Luminal  $\text{CO}_2$  diffuses back into the cell to complete the reabsorption cycle. In addition to this mechanism of transport, approximately 20% of filtered bicarbonate is reabsorbed passively along the paracellular pathway.<sup>[17]</sup>

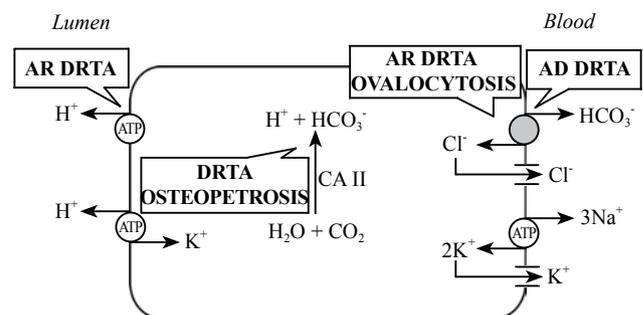
Hereditary isolated forms of type 2 RTA are extremely rare because this entity is usually seen in the context of more generalized dysfunctions of proximal tubule (Fanconi syndrome). The form of proximal RTA which is autosomal recessive and associated with ocular abnormalities results from inactivating mutations in the gene SLC4A4 localized in chromosome 4q21 and that encodes NBC1. Another rare form of autosomal recessive proximal RTA presents with distal RTA, osteopetrosis, cerebral calcification and mental retardation and is caused by CA II deficiency. The underlying defective gene is CA2 located in chromosome 8q22. The defective protein and gene responsible for the autosomal dominant proximal RTA only reported in a single Costa Rica family are unknown. It should be mentioned that there is a variant of transient sporadic isolated proximal RTA in infants, which is likely due to immaturity of the transport mechanisms.<sup>[18,19]</sup>

Distal urinary acidification occurs mainly in the  $\alpha$  intercalated cells of collecting tubules. The mechanism of  $\text{H}^+$  secretion coupled to bicarbonate reabsorption that takes place in the cortical collecting duct is schematically represented in the Fig.  $\text{H}^+$  secretes to the lumen by means of a vacuolar  $\text{H}^+\text{-ATPase}$  whose action is favored by the luminal electronegativity generated by  $\text{Na}^+$  reabsorption induced by aldosterone in the principal cells. There is also a  $\text{H}^+, \text{K}^+\text{-ATPase}$  but its physiologic role is probably more related to potassium than acid-base metabolism. Bicarbonate is transported from the cell to the blood by means of an electroneutral  $\text{Cl}^-/\text{HCO}_3^-$  anion exchanger (AE1). Cytoplasmic CA II facilitates hydration of  $\text{CO}_2$  to  $\text{H}_2\text{CO}_3$ . In the outer medullary collecting duct, there is no  $\text{Na}^+$  reabsorption. Therefore, the lumen is positively charged and  $\text{H}^+\text{-ATPase}$  must secrete  $\text{H}^+$  against an electrochemical gradient.<sup>[17]</sup>

Primary congenital forms of type 1 distal RTA

can be inherited following an autosomal recessive or autosomal dominant transmission. Autosomal dominant distal RTA is caused by heterozygous mutations in AE1 that cause intracellular retention or misplacement of the exchanger and, subsequently, loss of its function (Fig.).<sup>[20]</sup> The AE1 gene is completely sequenced and is designated as SLC4A1 on chromosome 17. From the clinical point of view, this variant of distal RTA is more frequently found in adults and its manifestations are usually less severe than those of distal RTA observed in early infancy. There is an autosomal recessive form of distal RTA associated with hemolytic anemia and ovalocytosis caused by mutations in AE gene. This variant has been described in a few kindred from Southeast Asia (Fig.).<sup>[21]</sup>

Sporadic or autosomal recessive forms of distal RTA caused by defects in the  $\text{H}^+\text{-ATPase}$  are the most frequently encountered in pediatric population (Fig.). The  $\text{H}^+\text{-ATPase}$  is a proton pump containing several subunits which are encoded by different genes. Loss of function mutations in the ATP6V1B1 gene that encodes the B1-subunit results in type 1 distal RTA associated with nerve deafness.<sup>[22]</sup> The ATP6V1B1 gene resides on chromosome 2 and it is expressed in the cochlea where the proton pump is presumably responsible for maintaining the pH of endolymph at 7.4. Abnormalities in pH and electrolyte composition of endolymph, a fluid physiologically low in  $\text{Na}^+$  and rich in  $\text{K}^+$ , damage hair cells and lead to severe sensorineural hearing loss. Loss of function mutations in the ATP6V0A4 gene that is located in chromosome 7 and encodes the a4 subunit of the proton pump cause distal RTA with preserved hearing.<sup>[21]</sup> However, the correlation between the genetic defect and the presence (ATP6V1B1) or absence (ATP6V0A4) of deafness is not so clear-cut, because some patients with mutations in ATP6V0A4 develop nerve deafness after the second decade of life, whereas some patients with mutations in ATP6V1B1 do not have the typical severe early-onset sensorineural deafness (personal observation).



**Fig.** Graphic representation of the acidification mechanism in the alpha intercalated cells of cortical collecting tubule and location of molecular defects in the different forms of autosomal dominant (AD) and autosomal recessive (AR) distal renal tubular acidosis (DRTA).

### Necessity for early recognition and diagnosis

Key guidelines on history and physical examination are summarized in the Table. The earlier RTA is recognized and diagnosed, the more successful the prevention of significant complications such as growth failure and nephrocalcinosis is ensured. These complications may regress with treatment except nephrocalcinosis does not regress easily even with correction of acidosis and diuretic treatment, especially in patients with type 1 RTA.

Review of the system may elicit other family members with similar symptoms or family history of hearing loss, osteopetrosis, ovalocytosis, Fanconi syndrome, etc.

RTA in infants usually presents with non-specific features of failure to thrive, polyuria, polydipsia, irritability, and recurrent vomiting from metabolic acidosis.<sup>[6,9,10]</sup> They are afebrile, unless there are intercurrent infections, and often the breathing pattern of tachypnea is the respiratory compensation to the metabolic acidosis.<sup>[6,9]</sup> Sometimes in the older RTA children with long-standing metabolic acidosis, the growth retardation may be striking and may be associated with rickets. In the adult patients, osteomalacia occurs instead of rickets. A common complaint in older patients is muscle weakness due to the neuromuscular effect of hypokalemia. This neuromuscular dysfunction may present as fatigue, constipation, myalgia, mild bone pain, and even severe muscular paralysis. The initial sudden, sharp pain from the kidney and ureteral stones may pass and turn into dull, occasional abdominal aches. Nephrocalcinosis may have no symptoms specific to the kidneys but progresses to chronic kidney failure silently with only proteinuria, microscopic hematuria, hypercalciuria and growth failure to serve as clues to the correct diagnosis of RTA.<sup>[9]</sup>

In contrast to the symptoms caused by the hypokalemic acidosis in type 1 and 2 RTA described above, hyperkalemia in type 4 RTA predominates over a mild metabolic acidosis.<sup>[16]</sup> The urinary sodium loss and potassium retention in type 4 RTA give rise

to the volume loss resulting from hypoaldosteronism (congenital adrenal hyperplasia) or aldosterone resistance (pseudohypoaldosteronism in infants, post obstructive uropathy in any age). Nephrocalcinosis and nephrolithiasis are uncommon in type 4 RTA<sup>[6]</sup> because of the high excretion of the calcium chelator, citrate.

The following laboratory procedures are needed to establish the diagnosis in the pediatrician's office:<sup>[6,9,23]</sup>

1) Fresh, spot urine pH: type 1 RTA urine pH consistently >5.5; type 2 RTA, urine pH consistently <5.5.

2) Serum electrolytes: serum total CO<sub>2</sub> <17.5 mEq/L (17.5 mmol/L) in all types of RTA, associated with hyperchloremic hypokalemia in type 1 and type 2 RTA and hyperkalemia in type 4 RTA.

3) Urinary anion gap [Na<sup>+</sup> + K<sup>+</sup> - Cl<sup>-</sup>] approximates renal NH<sub>4</sub><sup>+</sup> and differentiates RTA from diarrhea bicarbonate loss. The urinary anion gap is normal or positive if ammonium is increased, obligating urinary chloride to rise to balance the charges. When the urinary undetermined anion gap is negative, the charges are equal to ammonium excretion. When the undetermined anion gap is negative, extrarenal acidosis is suggested. When the undetermined anion gap is positive, RTA is suggested. These calculations are not useful in the presence of large bicarbonate or ketones in the urine.

The following tests will further characterize the associated renal tubular defects and assist in choosing therapeutic options:

1) 24 hours urine<sup>[9]</sup> for testing calcium, citrate, potassium and oxalate showed: hypercalciuria >4 mg/kg per day or urine calcium/creatinine ratio >0.21 mg/mg creatinine in adults; >0.4 mg/mg creatinine in patients at age of 19 months to 6 years and >0.6 mg/mg creatinine in patients at age of 7-18 months and >0.8 mg/mg creatinine in infants at age of less than 7 months. Hypocitraturia (<180 mg/g creatinine) characterizes type 1 RTA; hyperoxalaturia (>2 mg/kg per 24 hours) characterizes type 2 RTA.<sup>[9]</sup>

2) Ultrasonography of the kidney was done to rule out nephrocalcinosis, obstructive uropathy.<sup>[6]</sup> Ultrasonography should also be used to monitor the progress of these conditions.

3) Normal values for urine minus blood pCO<sub>2</sub> are >20 mmHg. Type 2 RTA is >20 mmHg, and primary type 1 RTA <20 mmHg.<sup>[9]</sup>

4) The serum concentrations of aldosterone and renin in type 4 RTA need to be established by the appropriate blood tests.<sup>[6]</sup>

The following tests are done in the nephrologist's office to define the various forms of RTA:

1) Tubular reabsorption of bicarbonate: In the presence of normal bicarbonatemia, bicarbonate wasting >15% in type 2 RTA and <5% in type 1 RTA.<sup>[6]</sup>

2) Tubular reabsorption of phosphate (TRP): In Fanconi syndrome and other secondary type 2 RTA,

**Table.** Key guidelines in history and physical examination

Careful history
Family history of RTA
Association with hearing loss
Osteopetrosis
Ovalocytosis
Secondary disorders, e.g., Fanconi syndrome
Physical examination
Height, weight, nutritional status
Hypertension
Nephrocalcinosis
Eyes
Bones

a TRP <60% confirms the renal tubular wasting of phosphate. In addition, aminoaciduria and potassium wasting, essential features of the Fanconi syndrome need to be confirmed.<sup>[6]</sup>

3) Renal acidification tests: If metabolic acidosis consistently present as characterized by total CO<sub>2</sub> <17.5 mEq/L (17.5 mmol/L), there is no need to further acidify the urine. If the metabolic acidosis is inconsistent, the renal ability to acidify can be maximally tested after ammonium chloride or arginine hydrochloride acid loading.<sup>[23]</sup> The net acid excretion of ammonium and titratable acid, exceeding 70 μEq/min per 1.73 m<sup>2</sup> confirms a distal tubular acidification defect.<sup>[10,23]</sup>

### Treatment of type 1 and type 2 RTA

To an infant or child with severe, symptomatic metabolic acidosis (serum CO<sub>2</sub> less than 12 mEq/L), treatment with intravenous bicarbonate solutions is given for a rapid repair according to the dosage formula: desired change in serum bicarbonate × body weight in kg × 0.6.

This assumes a bicarbonate distribution space of 60% kg body weight. Half of the dose can be given in the first 8 hours and the rest in the subsequent 24 hours. Serum potassium and calcium values need to be monitored and supplementation of these ions given as needed.<sup>[6]</sup>

In patients with moderate metabolic acidosis with serum bicarbonate concentrations of more than 12 and less than 17 mEq/L, instead of intravenous therapy, oral bicarbonate therapy will suffice.

Once the patient suffers from asymptomatic steady acidosis, workup including urine pH and other tests as delineated in the sections before may proceed. Thiazide and low sodium diet to decrease bicarbonate requirements and potassium supplements for hypokalemia as required round up the therapeutic regimens.

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 base.<sup>[6,9]</sup> Polycitra K solution contains potassium citrate to provide 2 mEq/ml of alkali and 2 mEq/ml of potassium, designed to correct both acidosis and hypokalemia.<sup>[6,9]</sup>

To maintain a stabilized correction of metabolic acidosis in infants and children with type 1, distal RTA, Santos et al<sup>[24]</sup> suggested a mean dose of 3.5 mEq/kg per day (range: 1 to 7 mEq/kg per day). The large variability in alkali requirements likely reflects medical non-compliance or associated proximal leak of bicarbonate in younger patients. Contrary to the expected higher dosage on a body weight basis in infants, there is no difference in dose requirements between infants and children.<sup>[24]</sup> Santos et al<sup>[24]</sup> also

found a significant increase in percentile weight and height in many treated children.

Type 2 RTA requires higher and more frequent doses of Bicitra. Sometimes, the dose is progressively increased to as high as 14 mEq/kg per day because of the large proximal tubular loss of bicarbonate. However, the possibility of non-compliance and discordance between what is prescribed and what is actually taken becomes a troubled clinical issue. When to aggressively increase the dose comes down to clinical judgment. The dilemma of continuing treatment with continued non-compliance is a long-term management challenge to overcome. The involvement of school nurses, parents, teachers and other resources is equally important. We have developed a section (vide infra) suggesting a strategy to compensate for patient non-compliance.

The potassium requirement decreases with correction of acidosis in type 1 RTA. In contrast, daily potassium requirement increases with correction of acidosis in type 2 RTA.<sup>[25]</sup> Because of urinary potassium wasting secondary to the heavier sodium (bicarbonate) load with treatment, hypokalemia may be life-threatening if compounded by the stress of undercurrent infections.

Renal phosphate wasting in type 2 RTA secondary to Fanconi syndrome needs careful phosphate replacement.

Hypercalciuria of type 1 RTA needs continued monitoring and thiazide diuretic to decrease urinary calcium excretion.

### Treatment of type 4 RTA

Patients with congenital adrenal hyperplasia require replacement treatment with fludrocortisone 0.1 to 0.3 mg/d (0.05 to 0.15 mg/m<sup>2</sup> per day).<sup>[6,9]</sup> Blood pressure needs to be monitored. Loop diuretic may be needed to increase potassium excretion. To reverse the hyperkalemia which characterizes the metabolic acidosis of type 4 RTA, all patients should be restricted to dietary potassium and some patients may need oral administration of potassium binders. To control hyperkalemia, another therapeutic option is to administer chlorothiazide and furosemide to increase renal excretion of potassium. Bicarbonate therapy of 1.5 to 2.0 mEq/kg per day is advocated to neutralize the metabolic acidosis.

### Compensation of patient non-compliance

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.<sup>[9]</sup> Probably all types of childhood RTA can benefit from this strategy for

better growth, and full dose of medication at least once or twice a day. Physiologically, the medication should be given every 6 hours to compensate for a rapid rate of urinary bicarbonate loss. But such a regimen is difficult to comply with in the long run. So giving a full or even extra large dose once or twice a day provides at least some compliance better than no compliance.

Teeth decay, sometimes blamed on the frequent bicarbonate and citrate administration, is a troubled, unresolved clinical issue at this point.

### Prognostic factors in RTA

For secondary RTA, the underlying disease determines the outcome. Patient compliance is a critical issue in this determination. Untreated, undiagnosed RTA obviously carries a poor outcome, often progressing to end-stage kidney failure from nephrocalcinosis.

Relatives should be screened for RTA and its treatment. The advances in understanding the gene mutation which give rise to some forms of RTA provide us with an opportunity for avoiding continued transmission of such gene defects.

**Funding:** This study was supported by National Institutes of Health grants: DK50419, DK07761 (JCMC) and by FIS C03/07, FIS PI051261, Fondos FEDER and Fundación Nutrición y Crecimiento (FS).

**Ethical approval:** Not needed.

**Competing interest:** No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**Contributors:** CJCM wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version. SF is the guarantor.

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Received October 30, 2006

Accepted after revision April 15, 2007