IN BRIEF

Clinical Approach to Renal Tubular Acidosis in Children

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Renal tubules are integral in maintaining fluid, electrolyte, and acid-base homeostasis. Various defects in tubular transport have been identified in all parts of the nephron, which can lead to renal tubular acidosis (RTA). RTA is characterized by normal serum anion gap hyperchloremic acidosis caused by the inability of the renal tubule to either reabsorb bicarbonate from the proximal tubule (proximal RTA [type II] [pRTA]) or adequately secrete hydrogen ions (distal RTA [type I] [dRTA]), combined pRTA and dRTA (type III RTA), or hypoaldosteronism (type IV) in the presence of normal or moderately impaired glomerular filtration rate. The diagnosis of RTA is made in the presence of low plasma bicarbonate concentration (<22 to 24 mEq/L [<22 to 24 mmol/L] in children and <20 to 22 mEq/L [<20 to 22 mmol/L] in infants), low blood P_{CO_2} level (<40 mm Hg in children and <35 mm Hg in infants), and normal anion gap in a nonhemolyzed sample. The diagnosis may be suspected in infants or young children with poor weight gain, polyuria, dehydration, and kidney stones. This article discusses the approach to the diagnosis and management of RTA in children.

dRTA/Type I RTA

dRTA is the most common type of primary RTA, characterized by the decreased secretion of hydrogen (H^+) ions due to the dysfunction of the intercalated cells in the distal convoluted tubules. H^+ ion secretion occurs mainly by trapping H^+ ions as ammonium ($NH4^+$) and through the titration of urinary buffers such as hydrogen phosphate. In systemic acidosis, the kidney responds by lowering the urine pH to a minimum of 4.5. In dRTA, the urine is inappropriately alkaline, with a pH higher than 5.5 despite metabolic acidosis.

The urine anion gap can be used to indirectly estimate urinary NH_4^+ because direct measurement of $NH4^+$ is challenging in the laboratory.

$$\text{Urinary AG (uAG)} = \text{urinary } [Na^+ + K^+ - Cl^-].$$

Under normal conditions, urine anion gap is negative, reflecting the unmeasured $NH4^+$. Hyperchloremic metabolic acidosis with a positive urine anion gap (>20 mEq/L [>20 mmol/L]) suggests low H^+ secretion and low $NH4^+$ excretion consistent with dRTA. A negative urine anion gap suggests extrarenal

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bicarbonate losses (eg, diarrhea). Chronic acidosis in dRTA leads to hypercalciuria and hypocitraturia, which may lead to medullary nephrocalcinosis and nephrolithiasis. In children, dRTA is most often observed as a primary or hereditary entity or may be acquired due to renal tubular damage from renal diseases, systemic conditions, or drugs. Causes of dRTA are listed in Table 1. Detailed family and medication histories with an emphasis on over-the-counter medications should be initiated at the first suspicion of RTA. Molecular genetic tests using next-generation sequencing techniques should be performed when a genetic form of RTA is suspected. If there are any physical examination findings suggestive of genetic causes or a family history of kidney involvement, genetic evaluation by a nephrologist or geneticist is recommended.

pRTA/Type II RTA

The primary defect in pRTA is bicarbonate wasting and resetting the threshold for bicarbonate reabsorption. The normal bicarbonate reabsorption threshold is 26 mEq/L (26 mmol/L) in adults and 22 mEq/L (22 mmol/L) in infants. It is reset to a much lower rate in type II RTA. For example, if the bicarbonate reabsorption threshold is set at 15 mEq/L (15 mmol/L), bicarbonate wasting occurs when this threshold is exceeded, and thereby, the plasma bicarbonate level is set at 15 mEq/L (15 mmol/L). Because the distal tubular and urinary acidification functions remain intact, these patients demonstrate appropriately acidified urine. With bicarbonate supplementation, the filtered bicarbonate threshold is exceeded, causing alkaline urine and high fractional excretion of bicarbonate, calculated as follows:

$$\text{Fractional excretion of bicarbonate (\%)} = \frac{\text{Plasma bicarbonate} \times \text{urine creatinine}}{\text{Urine bicarbonate} \times \text{plasma creatinine}} \times 100$$

pRTA in children can be either an isolated defect, which is rare, or part of generalized proximal tubular dysfunction known as Fanconi syndrome. Fanconi syndrome can impair tubular reabsorption of bicarbonate, phosphate, glucose, uric acid, low-molecular-weight proteins, and

Table 1. Causes of RTA

	TYPE I RTA (DISTAL RTA)	TYPE II RTA (PROXIMAL RTA)	TYPE IV RTA
Genetic/inherited	• Anion exchanger *(SLC4A1)* (autosomal dominant) • Hydrogen ion ATPase *(ATP6A1B1, ATP6A0V4)* (autosomal recessive)	X-linked recessive • Dent disease: chloride channel *(CLCN5, OCRL1)* • Lowe syndrome: phosphatidylinositol 4, 5-bisphosphate 5-phosphatase *(OCRL1)* Autosomal recessive • Cystinosis: cystinosin *(CTNS)* • Fanconi-Bickel: GLUT2 *(SLC2A2)* • Wilson disease: ATPase copper-transporting β-polypeptide *(ATP7B)* • Tyrosinemia: fumarylacetoacetate hydrolase *(FAH)* • Galactosemia: galactose-1-phosphate uridylyltransferase *(GALT)* • Hereditary fructose intolerance: fructose-1 phosphate aldolase *(ALDOB)* • Carbonic anhydrase II mutation	Aldosterone deficiency • Congenital isolated hypoaldosteronism • Congenital adrenal hyperplasia • X-linked adrenal hypoplasia *(NR0B1)* Aldosterone resistance • PHA type 1 o Systemic PHA type 1 *(SCNN1A, SCNN1C, SCNN1G)* o Renal PHA type 1 *(NR3C2)* • PHA type 2/Gordon syndrome (WNK1 and WNK4 kinases)
Acquired	• Graves disease • Sjogren syndrome • Systemic lupus erythematosus	• Sjogren syndrome • Acute lymphocytic leukemia • Multiple myeloma	• PHA type 3 or secondary PHA • Posterior urethral valve • Reflux nephropathy • Pyelonephritis • Interstitial nephritis • Sickle cell nephropathy
Medications	• Aminoglycosides • Amphotericin • Lithium	• Acetazolamide • Aminoglycosides • Cisplatin • Chinese herbs • Heavy metals (lead, cadmium, mercury, and copper) • Lamivudine • Outdated tetracyclines • Tenofovir • Valproic acid	• Angiotensin-converting enzyme inhibitors • Calcineurin inhibitors • Nonsteroidal anti-inflammatory drugs • Potassium-sparing diuretics • Trimethoprim

PHA=pseudohypoaldosteronism, RTA=renal tubular acidosis.

amino acids. Affected children classically present with metabolic acidosis, polyuria, polydipsia, hypophosphatemic rickets, glucosuria, hypouricemia, low-molecular-weight proteinuria, and aminoaciduria. The presence of multiple electrolyte derangements in addition to non–anion gap metabolic acidosis should lead physicians to consider a diagnosis of renal Fanconi syndrome. In the case of a suspected metabolic disorder, an evaluation for the underlying cause of Fanconi syndrome should be conducted by a nephrologist or geneticist (Table 2).

MIXED OR TYPE III RTA

Type III RTA has the features of both pRTA and dRTA and is rare in children. This can be associated with osteopetrosis where it is described as a loss of function of carbonic anhydrase II.

HYPERKALEMIC OR TYPE IV RTA

Type IV RTA is caused by selective aldosterone deficiency or intrinsic defects in the collecting duct that lead to aldosterone resistance (pseudohypoaldosteronism), resulting in impaired distal H^+ and potassium ion secretion, salt wasting, hyperkalemia, and metabolic acidosis (Table 2).

CLINICAL CLUES AND APPROACH TO RTA

RTA should be suspected in any child presenting with poor weight gain, polyuria, polydipsia (recurrent episodes

Table 2. Comparison of Different Types of RTA

VARIABLE	TYPE I RTA (DISTAL RTA)	TYPE II RTA (PROXIMAL RTA)	TYPE IV RTA
Clinical presentation	Usually isolated, autosomal recessive forms are associated with hearing loss	Usually as a part of a systemic disease, most often metabolic disease	Systemic or isolated
Metabolic acidosis	Severe, easy to control	Milder, difficult to control	Severe, easy to control
Urine pH	>5.5	<5.5	>5.5
Fractional excretion of bicarbonate	<5%	>15%	>15%
Serum potassium	Normal/low	Low	High
Tubular wasting	Absent	Variable presentation (aminoaciduria, proteinuria, glucosuria)	Absent
Bone defects	Severe (rickets, etc)	Variable	NA
Phosphaturia and hypophosphatemia	Absent	Present (variable)	NA
Hypercalciuria/nephrocalcinosis	Occasionally present	Often present	NA
Kidney stones	Frequently observed (calcium phosphate)	Rare	No
Renin and aldosterone	Unchanged	Unchanged	↑ Renin, ↑ aldosterone (PHA) ↓ Aldosterone (aldosterone deficiency) ↓ Renin and ↓ aldosterone (sickle cell nephropathy, chronic pyelonephritis, obstructive nephropathy)
Extrarenal features	Hemolytic anemia (autosomal dominant) Hearing loss (autosomal recessive)	Dent disease: rare, cataracts and intellectual disability (Dent II) Lowe syndrome: CNS, eyes Cystinosis: eyes, CNS, endocrine, gonadal Fanconi-Bickel: liver Wilson disease: liver, CNS, eyes Tyrosinemia: liver Galactosemia: CNS, eye, liver Hereditary fructose intolerance: liver	None
Management	Bicarbonate supplementation Stone management in case of kidney stones	Bicarbonate, phosphorus, and potassium supplements Hydration Cysteamine (cystinosis) Nitisinone (tyrosinemia) Cataract removal, glaucoma control, targeted rehabilitation therapy (Lowe)	Low-dose fludrocortisone therapy PHA type 1: sodium, fluids, and potassium-binding resins PHA type 2: thiazide diuretics PHA type 3: fluids, antibiotics

CNS=central nervous system, NA=not applicable, PHA=pseudohypoaldosteronism.

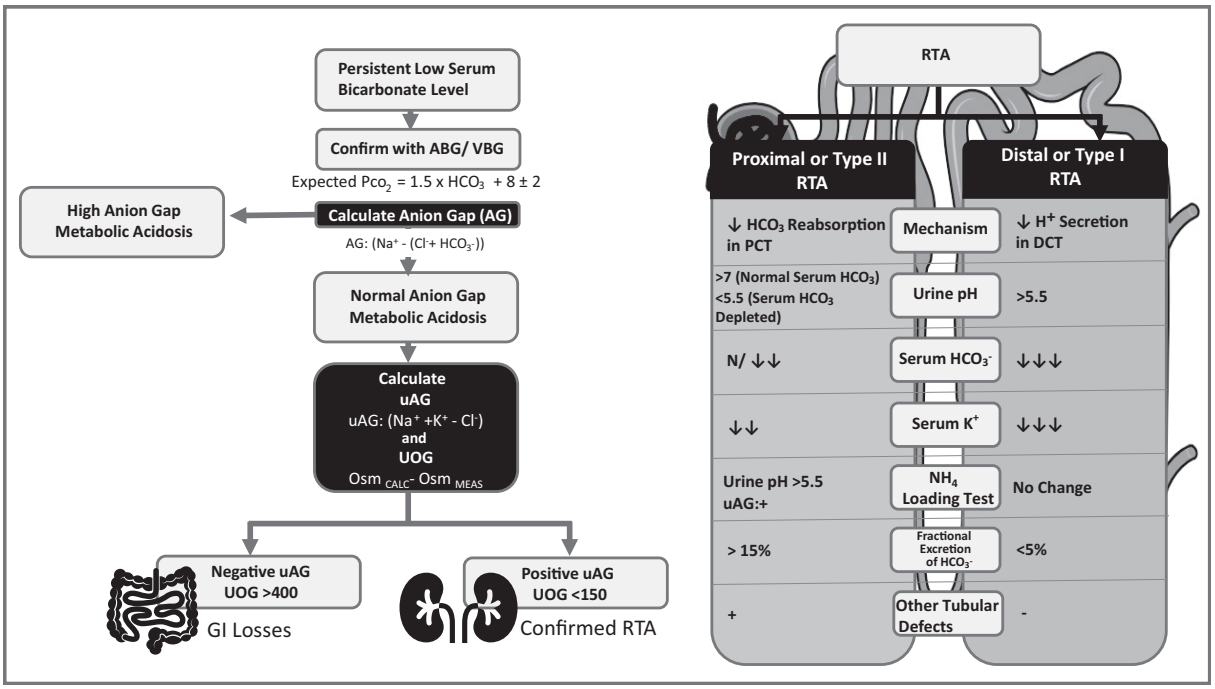

Figure. Approach to low serum bicarbonate level in a child. ABG/VBG=arterial/venous blood gas analysis, Cl^-=chloride ion, DCT=distal convoluted tubule, GI=gastrointestinal, H^+=hydrogen ion, HCO_3=bicarbonate, K^+=potassium ion, N/=, Na^+=sodium ion, PCT=proximal convoluted tubule, RTA=renal tubular acidosis, uAG=urine anion gap, UOG=urine osmolar gap. (Icons credit: Noun Project and BioRender.)

of dehydration in the absence of gastroenteritis illness; polyuria with dehydration), salt craving, symptoms of hypokalemia (sudden-onset hypotonia/weakness/paralysis after acute illness, abdominal distention, ileus, etc), tachypnea (secondary to metabolic acidosis), nephrocalcinosis or nephrolithiasis, resistant rickets, and vitamin A deficiency (night blindness, bitot spots, etc).

Referral to a pediatric nephrologist for formal RTA evaluation should be considered in a child with any of the previously mentioned features and with persistently (≥2 samples) low serum bicarbonate levels in a nonhemolyzed specimen (Fig), especially in the absence of gastrointestinal symptoms. Low serum pH and serum bicarbonate level should be confirmed via blood gas analysis. Once confirmed, calculation of the serum anion gap will establish whether the patient has elevated or normal anion gap metabolic acidosis. The urine anion gap and urine osmolar gap help differentiate gastrointestinal losses from renal causes of metabolic acidosis.

TREATMENT

Alkali therapy is the principal approach to correct acidosis. In pRTA, the magnitude of bicarbonate required to normalize serum bicarbonate may be as high as 10 to 30 mEq/kg per day, along with 1 to 5 mEq/kg per day of potassium supplements. Sodium bicarbonate or potassium citrate supplements aim to normalize blood pH and achieve bicarbonate levels greater than 20 mEq/L (>20 mmol/L) in infants and greater than 22 mEq/L (>22 mmol/L) in older children.

Potassium citrate (Polycitra-K® liquid [PAI Pharma, Greenville, SC] or UroCit®-K pills [Mission Pharmacal Co, San Antonio, TX]) is the preferred supplement because it corrects both hypokalemia and hypocitraturia. Patients with Fanconi syndrome may also require potassium, phosphate, and vitamin D supplementation in addition to specific therapy targeting the underlying cause.

Most genetic forms require lifelong supplementation and ongoing subspecialist care. Milder varieties may learn to supplement via diet, such as increasing consumption of potassium-rich foods or citrate-rich foods (citrus fruits, melons, etc). In children, dietary protein restriction is not recommended except in tyrosinemia. Genetic diseases such as cystinosis and tyrosinemia require lifelong treatment with oral cysteamine and nitisinone, respectively.

Therapy for hyperkalemic RTA is directed toward treating the underlying etiology. In medication-induced RTA, discontinuation of the offending medication is necessary. Patients with obstructive uropathy require relief of obstruction and hydration with normal saline.

Summary

RTA occurs due to the kidneys' failure to maintain acid-base homeostasis by the inability to excrete H^+ ions (dRTA), reabsorb bicarbonate from proximal tubules (pRTA), or dysfunction of the renin-angiotensin-aldosterone axis (hyperkalemic RTA). RTA can lead to poor weight gain, polyuria, rickets, and nephrocalcinosis. Treatment includes supplementation with sodium bicarbonate or potassium citrate. Patients with pRTA and Fanconi syndrome may also require phosphate and vitamin D supplements. Hyperkalemic RTA therapy depends on addressing the underlying cause. Molecular genetic tests using next-generation sequencing techniques should be performed when a genetic form of RTA is suspected.

Comment: Although I remembered to consider RTA for young children with poor weight gain who had low bicarbonate levels, I would sometimes mix up the different types. This In Brief clearly differentiates the different types. It also emphasizes additional reasons to differentiate due to varying treatments and etiologies, as some etiologies need to be pursued with genetic testing and may require lifelong treatment. I have also found it helpful to collaborate with a pediatric nephrologist to assist with treatment options and provide the best care possible.

Janet R. Serwint, MD
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ANSWER KEY FOR NOVEMBER PEDIATRICS IN REVIEW

Clinical Care of Acne Vulgaris for Transgender and Gender Diverse Youth: 1. B; 2. E; 3. E; 4. E; 5. E.
Cleft Lip and Palate and Isolated Cleft Palate: 1. C; 2. D; 3. D; 4. D; 5. E.
Vascular Pathology: Three Patient Cases: 1. B; 2. B; 3. D; 4. D; 5. D.