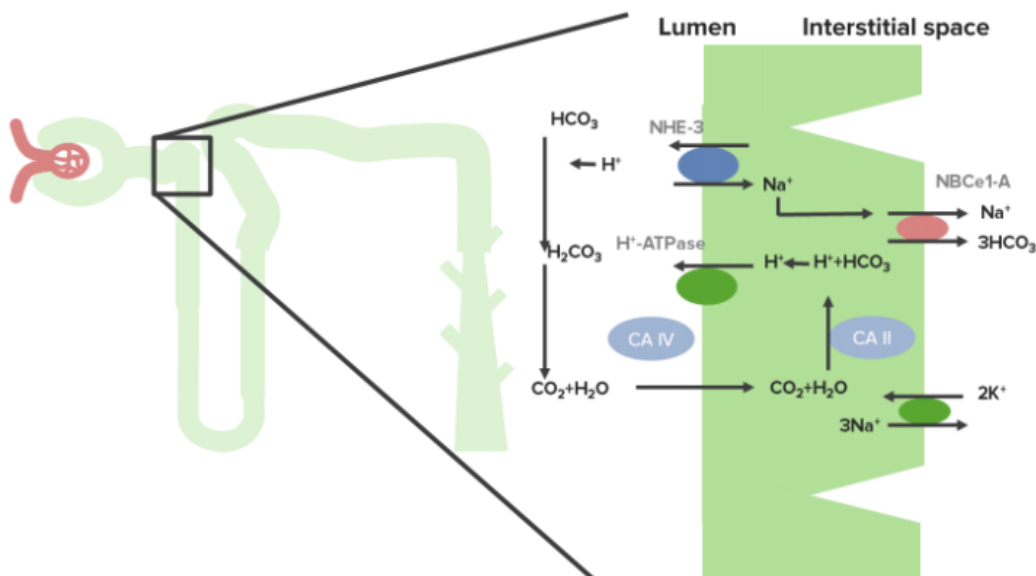


# Renal Tubular Acidosis Type 2 and 3: Proximal Renal Tubular Acidosis (pRTA) and Combined Proximal and Distal RTA in Children

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**Renal tubular acidosis (RTA) type 2, also called proximal renal tubular acidosis, is characterized by hyperchloremic metabolic acidosis due to the impaired reabsorption of bicarbonate ( $\text{HCO}_3^-$ ) in proximal tubules. It can be due to an isolated defect or part of a generalized defect (Fanconi syndrome).**

**Rickets/Osteomalacia is more common and treatment is usually difficult. RTA type 3 is designated when the combined features of both type 1 and type 2 RTA are present. In this article, the etiology, pathophysiology, symptoms, diagnosis, differential diagnosis, treatment and prognosis of renal tubular acidosis type 2 are described.**



## Definition

Renal tubular acidosis is a group of disorders characterized by the failure of kidneys to reabsorb the bicarbonate ion and excretion of hydrogen ion resulting in acidosis and hypokalemia.

Proximal RTA, also called RTA type 2, is characterized by an impaired proximal tubular acidification mechanism in the kidneys, which is due to a reduced reabsorption of  $\text{HCO}_3^-$  in proximal tubules. Term RTA type 3 is used when features of both type 1 and type 2 RTA are present.

# Epidemiology of Renal Tubular Acidosis Type 2 and 3

The exact prevalence of RTA type 2 and type 3 are unknown. It may occur as a single entity or a part of a generalized dysfunction (e.g. Fanconi's syndrome). Isolated primary proximal RTA is rare. Type 3 RTA is extremely **rare**.

## Etiology of Renal Tubular Acidosis Type 2 and 3

### Isolated proximal acidification defect

Primary causes:

- Sporadic forms
- Inherited forms:
  - Autosomal dominant form: Defect in NHE3, associated with short stature and **osteomalacia**.
  - **Autosomal recessive form**: Defect in CA-II, associated with cerebral calcification and mental retardation.
  - **Autosomal recessive form**: Defect in NBC1, associated with mental retardation, ocular manifestations (band keratopathy, cataract, and glaucoma), short stature, defective teeth, and basal ganglia calcification.
- Transient phenomenon during infancy.

### Secondary causes (carbonic anhydrase deficiency)

- **Drugs**: Acetazolamide, sulfanilamide, and mafenide

### Generalized PCT defect (Fanconi syndrome)

Primary causes:

- Inherited renal disease (Idiopathic Fanconi).
- Cystinosis, Wilson disease – the most common causes.
- Tyrosinosis, metachromatic leukodystrophy, glycogen storage disease type 1.
- Hereditary fructose intolerance, galactosemia.
- **Low syndrome (oculocerebrorenal syndrome)**: X-linked disorder associated with congenital cataract and mental retardation (OCRL gene mutation).
- **Dent disease**: X-linked recessive disorder associated with tubular proteinuria, hypercalciuria, **nephrocalcinosis**, and **nephrolithiasis** (chloride channel gene CLCN5 or OCRL gene mutation).
- **Fanconi-Bikel syndrome**: Autosomal recessive disorder associated with impaired utilization of glucose and galactose.

Secondary causes:

- **Calcium metabolism disorders**: Vitamin D dependent rickets, vitamin D resistant rickets.
- **Immunoglobulin Disorders**: Amyloidosis, monoclonal gammopathy of undetermined significance (MGUS), light chain deposition disease (LCDD), multiple myeloma, cryoglobulinemia.

- **Tubulointerstitial diseases:** Medullary cystic disease, Sjogren syndrome, renal transplant rejection, Balkan nephropathy.
- **Drugs and other compounds:** Outdated tetracyclines, gentamicin, valproic acid, ifosfamide, cisplatin, streptozotocin, heavy metals (lead, mercury, cadmium), toluene, tenofovir.
- **Miscellaneous:** Nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, hyperparathyroidism, burns, chronic renal vein thrombosis, hypokalemic nephropathy, **kwashiorkor**.

Remember, conditions that can cause both proximal RTA and distal RTA include amyloidosis, multiple myeloma, medullary cystic disease, renal transplant rejection, and ifosfamide.

### Type 3 RTA:

- Autosomal recessive form: In association with osteopetrosis, cerebral calcification, and mental retardation (loss-of-function mutations in the gene encoding carbonic anhydrase II).

## Pathophysiology of Renal Tubular Acidosis Type 2 and 3

Important renal mechanisms for maintaining acid-base homeostasis include reabsorption of filtered  $\text{HCO}_3^-$  and excretion of nonvolatile acids. Normally, 85—90% of  $\text{HCO}_3^-$  is reabsorbed in proximal tubules and distal segments cause acidification of urine by the reclamation of the remaining  $\text{HCO}_3^-$  and by active secretion of  $\text{H}^+$  in the form of titrable acid,  $\text{NH}_4^+$ , and free ions.

In **proximal convoluted tubule (PCT)**, luminal  $\text{Na}^+/\text{H}^+$  exchanger (NHE3),  $\text{Na}^+/\text{K}^+$  ATPase, brush border carbonic anhydrase IV (CA-IV), cytoplasmic carbonic anhydrase II (CA-II) and basolateral  $\text{Na}^+-3\text{HCO}_3^-$  cotransporter (NBC1) play an important role in  $\text{HCO}_3^-$  reabsorption.  $\text{Na}^+/\text{K}^+$  ATPase creates negative potential, which favors  $\text{Na}^+$  reabsorption, which is coupled to  $\text{H}^+$  secretion by NHE3. Luminal CA-IV produces  $\text{CO}_2$  and  $\text{H}_2\text{O}$  from the secreted  $\text{H}^+$  and luminal  $\text{HCO}_3^-$ .  $\text{CO}_2$  diffuses into cells of PCT and cytoplasmic CA-II reforms  $\text{H}^+$  and  $\text{HCO}_3^-$ . The  $\text{HCO}_3^-$  is reabsorbed into the systemic circulation by basolateral  $\text{Na}^+-3\text{HCO}_3^-$  cotransporter.

Proximal  $\text{HCO}_3^-$  reabsorption is increased by high luminal  $\text{HCO}_3^-$  concentration, high luminal  $\text{PCO}_2$ , increased NHE3 activity (low extracellular fluid volume,  $\alpha$ -adrenergic stimulation, renin-angiotensin-aldosterone axis activation), **glucocorticosteroids**, increased luminal electropositivity (high parathormone levels), etc. PCT also synthesizes and secretes  $\text{NH}_4^+$  which is an important buffer.

In **proximal RTA**, there is defective reabsorption of  $\text{HCO}_3^-$  in proximal tubules due to a defect in one of above mechanisms or due to the generalized defect in proximal tubular function (Fanconi syndrome). As a result, threshold serum  $\text{HCO}_3^-$  concentration for reabsorption of  $\text{HCO}_3^-$  from PCT is reduced to less than 15 mEq/L. Ammonia secretion and  $\text{H}^+$  secretion are intact in proximal RTA.

Loss of  $\text{HCO}_3^-$  results in **non-anion gap metabolic acidosis (NAGMA)**. The lost  $\text{HCO}_3^-$  is also accompanied by a cation ( $\text{K}^+$  more than  $\text{Na}^+$ ). A loss of  $\text{Na}^+$  causes polyuria and volume depletion, which increases thirst and activates renin-angiotensin-aldosterone (RAA) axis. **Aldosterone** increases  $\text{Na}^+$  reabsorption, which causes blunting of

hypovolemia and increases  $K^+$  excretion, which aggravates hypokalemia. Increased distal  $Na^+$  increases distal  $Ca^{2+}$  wasting, causing **hypercalciuria**.

**Hypophosphatemia** and **phosphaturia** contribute to **rickets**. Bone mineralization without rickets may also be seen.

In **Fanconi syndrome**, due to a generalized PCT defect, there is a urinary loss of bicarbonate, low-molecular-weight protein, uric acid, glucose, phosphate, citrate, calcium, potassium, and amino acids.

Some children with RTA show features of both type 1 and type 2 RTA and hence are diagnosed with type 3 RTA; however, many of them exhibit features of proximal RTA only transiently and evolve into classic distal RTA later. Features of proximal RTA in these children are thought to be due to the immaturity of proximal tubule only; hence, some authorities do not consider type 3 RTA as a distinct entity.

## Symptoms of Renal Tubular Acidosis Type 2 and 3

Children with proximal RTA may be asymptomatic or they may present with symptoms like **polyuria** and **polydipsia**. Muscle weakness, fatigue, hypotonia, and constipation may be present due to hypokalemia. Anorexia, vomiting, and dehydration may also be present. Low normal blood pressure is seen due to **hypovolemia**.

**Refractory rickets** or **osteomalacia** is often present, which may be associated with pathological fractures, bone pain, growth retardation, and **osteopenia**. Growth retardation and a failure to thrive may be seen in children. Unlike distal RTA, **nephrolithiasis** is absent in proximal RTA.

If associated with the specific syndrome, additional signs and symptoms of the syndrome are present.

## Diagnosis of Renal Tubular Acidosis Type 2 and 3

A hallmark of RTA is **non-anion gap metabolic acidosis (NAGMA)** or **hyperchloremic metabolic acidosis**. Important laboratory findings in proximal RTA are low serum  $HCO_3^-$ , hypokalemia (although less severe than that in distal RTA), and variable urinary pH. There may be increased or normal excretion of calcium, citrate, or phosphate in the urine, while there may be decreased or normal excretion of  $NH_4^+$  in the urine. Serum calcium and serum phosphate are normal. **(High-yield information.)**

**Urine anion gap (UAG)** is variable, usually negative in proximal RTA.

**Urine pH more than 5.5** suggests a renal acidification defect when the pH is measured in a fresh early morning urine sample.

Urine pH is variable in proximal RTA. Urine is alkaline if serum  $HCO_3^-$  concentration is more than tubular maximum, while urine pH is less than 5.3 when serum  $HCO_3^-$  concentration is less than the tubular maximum. Remember that RTA type II and RTA type IV can present with urine pH < 5.5. **(High-yield information.)**

On performing an **ammonium chloride acid loading test**, urine pH decreases to less than 5.3 in proximal RTA, which helps to differentiate it from distal RTA.

In proximal RTA, the measurement of urine pH after administration of **furosemide** also shows a decreased urine pH; however, there are high rates of false-positive and false-

negative results in this test.

On performing a **sodium bicarbonate loading test**, urine  $\text{PCO}_2$  is normal (more than 60-70 mm Hg), urine-blood  $\text{PCO}_2$  gradient (U-B  $\text{PCO}_2$ ) is more than 20 mm Hg, and fractional excretion of bicarbonate ( $\text{FEHCO}_3$ ) is more than 10-15% in proximal RTA.

In Fanconi syndrome, bicarbonaturia, tubular proteinuria, uricosuria, glycosuria, phosphaturia, citraturia, and aminoaciduria are present.

## Differential Diagnoses of Renal Tubular Acidosis Type 2 and 3

- Other types of RTA
- Other causes of NAGMA
  - Chronic renal failure
  - Extrarenal bicarbonate loss – diarrhea, intestinal fistula, etc
  - Ketoacidosis
  - Lactic acidosis
  - Exogenous administration of  $\text{Cl}^-$ -rich solutions
  - Parenteral nutrition
  - Drug toxicity

## Therapy of Renal Tubular Acidosis Type 2 and 3

In proximal RTA, the goal of treatment is to increase serum  $\text{HCO}_3^-$  to as close to normal as possible; however, this is usually difficult because of increased **bicarbonaturia**, **polyuria**, and **hypokalemia** associated with bicarbonate administration, due to decreased bicarbonate tubular maximum.

Due to a massive loss of bicarbonate, children with proximal RTA require higher (as high as 10-20 mEq/kg/day) and more frequent doses of oral alkali, in the form of **sodium bicarbonate** or **sodium citrate** solution.

Supplementation with potassium and vitamin D is usually required in proximal RTA. As renal activation of vitamin D is defective, **calcitriol** is the preferred form for vitamin D supplementation. Phosphate replacement may be required in Fanconi syndrome due to phosphate wasting.

**Thiazide diuretics** are useful in the treatment of proximal RTA as they induce mild volume depletion, enhance proximal reabsorption of sodium, and therefore secondarily enhance the reabsorption of  $\text{HCO}_3^-$ .

Children with **severe metabolic acidosis** (serum bicarbonate less than 12 mEq/L) are given intravenous bicarbonate, after calculation of the required dose of bicarbonate. Half of the required dose is administered over 8 hours and the remaining half dose is administered over the next 24 hours. The required dose is calculated using the following formula:

Required dose = desired change in serum bicarbonate x body weight (kg) x 0.6.

# Progression and Prognosis of Renal Tubular Acidosis Type 2 and 3

In proximal RTA, although improvement in growth and reduced severity of bone disease are observed with the correction of acidosis, the overall improvement is less impressive in children. Patients with systemic illness experience significant morbidity.

**Hyperchloremic acidosis** is considered to be a risk factor for the development of **acute kidney injury** (AKI) following abdominal surgery.

## Complications

Complications may include:

- Rickets
- Osteomalacia
- Failure to thrive
- Kidney stones
- Renal cyst formation

## References

Sreedharan R, Avner ED. Renal Tubular Acidosis. In: Kliegman RM, Stanton BF, ST Geme III JW, Schor NF, Editors. Nelson Textbook of Paediatrics, 20<sup>th</sup> edition. Elsevier, Philadelphia: 2016. PP. 3848-51.

Basu G, Sudhakar G, Mohapatra A. Renal tubular acidosis. Clinical Queries Nephrology 2013; 2: 166-78.

Soleimani M, Rastegar A. Pathophysiology of Renal Tubular Acidosis: Core Curriculum 2016. American Journal of Kidney Diseases 2016.

<http://emedicine.medscape.com/article/240809-overview>

**Correct answers:** 1B; 2C; 3E

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