Renal Tubular Acidosis

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Renal tubular acidosis is a relatively uncommon clinical syndrome characterized by the inability of the kidney to adequately excrete hydrogen ions, retain adequate bicarbonate, or both. This syndrome can be categorized into 3 separate disorders, each with unique clinical characteristics. Although an uncommon finding, prompt and inexpensive tests can lead to early intervention and subsequently reduce complications from persistent renal dysfunction. The purpose of this article was to bring awareness of the clinical manifestations, diagnosis, and treatments of renal tubular acidosis to critical care nurses.

Keywords: Renal disease, Renal physiology, Renal tubular acidosis

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INTRODUCTION AND BACKGROUND

Renal tubular acidosis (RTA) is a relatively uncommon clinical syndrome characterized by the inability of the kidney to adequately excrete hydrogen ions, retain adequate bicarbonate, or both.¹,² First illustrated in 1935, this syndrome was further delineated as RTA in 1951.² Renal tubular acidosis syndrome is manifested in the presence of a relatively normal glomerular filtration rate, normal plasma anion gap, and a hyperchloremic metabolic acidosis.²,⁴ Renal tubular acidosis can additionally be categorized into 3 separate disorders, each with unique clinical characteristics. The 3 disorders include (1) proximal RTA (type 2), (2) distal RTA (type 1), and (3) hyperaldosteronism-associated RTA (type 4). Although an uncommon finding, prompt and inexpensive tests can lead to targeted intervention and reduce complications from persistent renal dysfunction. The purpose of this article was to bring awareness of the clinical manifestations, diagnosis, and treatments of RTA to critical care nurses. Two case studies illustrate the crucial elements in the diagnosis and subsequent treatment of RTA.

CASE STUDIES

Ruling in RTA

A 46-year-old white woman presented to the emergency department with complaints of progressively worsening general weakness over the past month. Examination results were relatively benign aside from general, diffuse muscle weakness, dry buccal mucosa, and dry eyes. Her medical and surgical history were unremarkable except for an approximate 6-month history of dry eyes that was unrelieved by over-the-counter eye drops. Her current medications were only over-the-counter eye drops (artificial tears). She denied any known allergies to medications and denied the use of alcohol or tobacco products. Laboratory testing revealed the following:

- Chemistry: sodium (Na⁺), 135 mmol/L; potassium (K⁺), 2.1 mmol/L; chloride (Cl⁻), 112 mmol/L; phosphate (PO₄²⁻), 2.6 mg/dL; blood urea nitrogen (BUN), 15 mg/dL; creatinine (Cr), 0.9 mg/dL; calcium (Ca²⁺), 9.4 mg/dL; carbon dioxide, (CO₂) 15 mmol/L.
- Arterial blood gas: pH 7.28; PCO₂, 47 mm Hg; HCO₃⁻, 16 mmol/L; PO₂, 120 mm Hg.
- Urinalysis: pH 7.1
- Sodium, urine random: 82 mEq/L
- Potassium, urine random: 26 mEq/L
- Chloride, urine random: 78 mEq/L
- 24-Hour urinary anion gap 30

Further diagnostic testing included a positive rheumatoid factor (IgM) and positive anti–Ro/SS-A. Through an ophthalmologist referral, a diagnosis of bilateral keratoconjunctivitis...
sicca was made. Subsequent salivary gland biopsy of the lower lip confirmed Sjögren syndrome as the presenting diagnosis. The patient was diagnosed as having Sjögren syndrome associated with hypokalemia and distal RTA. Although Sjögren syndrome primarily affects women older than 40 years and those with a family history of Sjögren syndrome, it is a relatively uncommon clinical disorder.\(^2\)

The patient was diagnosed as having Sjögren syndrome associated with hypokalemia and distal RTA.

**Ruling Out RTA**

A 66-year-old white woman presented to the emergency department with a 1- to 2-day history of mental status change, confusion, lethargy, and 3-day history of nausea and diarrhea. Her medical history was significant for bladder cancer with multiple bladder surgeries, ileal conduit, recurrent urinary tract infections (UTIs), chronic obstructive pulmonary disease, and bipolar disorder. Her current medications include albuterol, dicyclomine (Bentyl), clonazepam, venlafaxine hydrochloride (Effexor), loperamide (Imodium), potassium, mirtazapine (Remeron), quetiapine (Seroquel), carbamazepine (Tegretol), and trazodone. She had no known allergies to medications. She reported use of alcohol in the past but denied alcohol or tobacco use within the past 12 months.

Further questioning revealed approximately 6 to 8 episodes of large, liquid stools for the past 3 days despite self-treatment with Imodium. She reported the stool to be light brown in color, without obvious blood. She denied abdominal pain, vomiting, and recent weight loss, but admitted to a poor appetite over the past few days. Upon physical examination, she was found to be drowsy yet oriented. She was pale and thin in appearance. Initial vital signs displayed a pulse rate of 110 beats per minute, blood pressure of 90/54 mm Hg, and a respiratory rate of 18 breaths per minute. The monitor displayed sinus tachycardia. Lungs were clear to auscultation, and her abdomen was nontender and flat, with hyperactive bowel sounds. An ileal conduit was noted to her right lower abdomen, drain bag intact, with a small amount of cloudy, amber urine present. Initial laboratory testing was obtained, which revealed the following:

- Chemistry: Na\(^+\), 136 mmol/L; K\(^+\), 2.0 mmol/L; Cl\(^-\), 120 mmol/L; HCO\(_3^-\), 19 mmol/L; PO\(_4^{3-}\), 1.1 mg/dL; BUN, 29 mg/dL; creatinine, 1.0 mg/dL; Ca\(^{2+}\), 10.6 mg/dL
- Serum anion gap: 7
- Complete blood count: white blood cells, 8K/μL; hemoglobin, 11.8 g/dL; hematocrit, 35.3%; platelet, 379 K/μL
- Clostridium difficile—positive stool antigens
- Urinalysis: positive for leukoesterase and nitrogen, pH 7.2

She was subsequently admitted to the intensive care unit with the diagnosis of change in mental status due to dehydration, C difficile, UTI, hypophosphatemia, and hypokalemia. The treatment plan included a course of antibiotics for her UTI and C difficile, intravenous rehydration with 0.9% saline, and replacement of both potassium and phosphorous.

Over the course of her hospitalization, the frequency of stools decreased, but she became increasingly somnolent. Further laboratory testing revealed the following:

- Chemistry: Na\(^+\), 157 mmol/L; K\(^+\), 2.7 mmol/L; Cl\(^-\), 144 mmol/L; HCO\(_3^-\), 8 mmol/L; BUN, 47 mg/dL; creatinine, 1.2 mg/dL; Ca\(^{2+}\), 2.7 mmol/L; PO\(_4^{3-}\), 1.4 mg/dL
- Serum anion gap: 5
- Complete blood count: white blood cell, 12.8; hemoglobin, 11.5; hematocrit, 33.9; platelet, 142
- Arterial blood gas: pH 7.27; PCO\(_2\), 19 mm Hg; HCO\(_3^-\), 9 mmol/L; PO\(_2\), 149 mm Hg
- Sodium, urine random: 45 mEq/L
- Potassium, urine random: 11 mEq/L
- Chloride, urine random: 61 mEq/L
- Urinary anion gap: −27

The laboratory results illustrated a hyperchloremic, non-anion gap metabolic acidosis. The differential diagnoses for her presenting laboratory results and physical examination included renal or gastrointestinal (GI) wasting via diarrhea, proximal RTA, distal RTA, primary hyperparathyroidism, aldosterone deficiency, Addison disease, aldosterone insensitivity, and/or ureteroileostomy.\(^6\) To rule out a blockage to her ileal conduit, an ileal conduit loopogram was obtained with results of no extraluminal contrast observed (negative). The result of her urinary anion gap ([urine Na\(^+\) + urine K\(^+\)] − urine [Cl\(^-\)])\(^2,4\) was normal (−27), supporting a diagnosis of GI wasting via diarrhea as being a likely cause of her hyperchloremic, non-anion gap metabolic acidosis. Her serum bicarbonate corrected over the following days with an intravenous administration of dextrose with sodium bicarbonate, while continuing to replete her potassium and phosphorous. Over the following week, she became increasingly alert, had minimal diarrhea, and was eventually transferred to the floor.

**PATHOGENESIS**

**Renal Acidification**

The kidneys play a vital role in the homeostasis of acid-base balance throughout the body. This role is mainly seen through both the proximal convoluted tubule and the distal nephron. With normal, steady-state conditions,
approximately 0.8 to 1 mEq per kilogram of nonvolatile acid is generated daily, primarily as a by-product of metabolism from dietary protein. This acid load is excreted through the urine in the presence of sufficient buffering compounds, which include ammonia and phosphate. As the systemic acid load increases, there is a subsequent increase in ammonium production and excretion. Failure to excrete adequate amounts of ammonium directly contributes to the development of metabolic acidosis.

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Proximal Tubule
The proximal convoluted tubule reabsorbs filtered bicarbonate and hydrogen ion secretion; 80% to 90% of the total filtered bicarbonate is reclaimed here. Failure of this reclamation leads to a decrease in systemic base and a subsequent metabolic acidosis.

Distal Tubule
The distal tubule secretes acid via hydrogen molecules through an H⁺-ATPase pump. Typically, only a small portion, 10% to 20%, of the filtered bicarbonate reaches the distal tubule. In addition, the secreted hydrogen ions work to titrate ammonia, phosphate, and urinary buffers, leading to excretion of common urinary acids. Therefore, when the distal tubule is unable to adequately secrete hydrogen, a resulting acid-base disequilibrium can lead to a tremendous and overwhelming acidemia.

CLINICAL PRESENTATION

Proximal RTA (Type 2)
Proximal RTA, the least common form of RTA, is secondary to impaired bicarbonate reabsorption in the proximal tubule and decreased ammonium excretion. The threshold for bicarbonate in proximal RTA is typically decreased to 15 mmol/L or greater. Therefore, if serum bicarbonate decreases below this threshold, fractional bicarbonate excretion decreases and urinary pH is lowered below 5.5. Usually, a moderate presentation of metabolic acidosis is apparent. However, large amounts of alkali supplementation therapy may be necessary. The additional clinical finding of renal potassium wasting is often problematic for the clinician. Renal tubular acidosis can occur either as an isolated syndrome (rare) or in conjunction with another transport defect, as in Fanconi syndrome. Both inherited and secondary (acquired) disorders for proximal RTA are listed in Table 1. Inherited disorders, which result in accumulation of endogenous metabolites and subsequent tubular injury, include Wilson disease, cystinosis, tyrosinemia, fructose intolerance, glycogen storage disease type I, Lowe syndrome, and galactosemia, which are all related to Fanconi syndrome. Fanconi syndrome is thought to be directly associated with a deficit in ATP production in the proximal tubule, subsequently reducing the activity of the sodium-potassium adenosine triphosphatase, an enzyme needed for normal cellular pump function. Chief characteristics of Fanconi syndrome include glycosuria, hyperphosphaturia, hyperuricosuria, hypercalciuria, and aminoaciduria. Other common presentations include osteomalacia or osteopenia secondary to the associated phosphaturia and deficiency in calcitriol. Paroxysmal nocturnal hemoglobinuria can also be seen in Fanconi anemia, with iron deposition found in proximal tubule cells.

Acquired disorders resulting in proximal RTA typically present secondary to toxic or immunologic damage to the nephron. Toxins may include heavy metals, outdated tetracycline, and ifosfamide. Presentation of proximal RTA may also include light-chain nephropathy secondary to multiple myeloma. However, this nephropathy is typically accompanied by the Fanconi syndrome and may be

TABLE 1 Conditions Associated With Proximal and Distal Renal Tubular Acidosis (RTA)

<table>
<thead>
<tr>
<th>Proximal RTA (Type 2)</th>
<th>Distal RTA (Type 1)</th>
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<tbody>
<tr>
<td>Inherited</td>
<td>Acquired</td>
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<tr>
<td>Wilson disease</td>
<td>Heavy metal poisoning</td>
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<tr>
<td>Cystinosis</td>
<td>Outdated tetracycline use</td>
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<tr>
<td>Tyrosinemia</td>
<td>Ifosfamide use</td>
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<tr>
<td>Fructose intolerance</td>
<td>Carbonic anhydrase inhibitor use</td>
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<td>Glycogen storage disease type I</td>
<td>Multiple myeloma</td>
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<td>Lowe syndrome</td>
<td>Lithium use</td>
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<tr>
<td>Galactosemia</td>
<td>Toluene use</td>
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<tr>
<td>Fanconi syndrome</td>
<td>Amphotericin B use</td>
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evident prior to signs of myeloma.\textsuperscript{12} Carbonic anhydrase inhibitors, specifically acetazolamide, used in the treatment of glaucoma, have also been linked to proximal RTA and are typically the most common medications associated with proximal RTA.\textsuperscript{9,10,12} Distal RTA (Type 1) Whereas distal RTA is relatively uncommon in the Western population, it is increasingly common in areas across the world with high rates of parental consanguinity.\textsuperscript{13} Distal RTA is characterized by the inability of the kidneys to acidify the urine to a pH less than 5.5 with a concurrent metabolic acidosis.\textsuperscript{3,8} Distal RTA is often secondary to the impaired ability of the distal tubule to secrete hydrogen ions.\textsuperscript{8,13} Disease states that may lead to a decrease in distal hydrogen ion secretion include low hydrogen–adenosine triphosphatase pump activity, back-leak of hydrogen, or impairment in distal sodium reabsorption,\textsuperscript{10} which may be related to primary and secondary disorders, as displayed in Table 1. In all forms of distal RTA, the excretion of ammonium is decreased.\textsuperscript{9} Usual disease states that lead to low hydrogen–adenosine triphosphatase pump activity include inherited disorders, autoimmune disease, medullary interstitial disease, toxins, or drugs. Inherited disorders include sickle cell disease; Marfan syndrome; Ehlers-Danlos, a rare disease that affects the synthesis of collagen\textsuperscript{14}; and Wilson disease, an autonomic-recessive disorder resulting in the accumulation of copper in the liver, brain, kidney, and cornea.\textsuperscript{15} Autoimmune diseases, including lupus, rheumatoid arthritis, forms of chronic active hepatitis, and Sjögren syndrome, are also causes of distal RTA and are associated with genetic mutations.\textsuperscript{10,12} Sjögren syndrome leads to a distal tubule acidification of filtrate in approximately 25% of patients.\textsuperscript{12,16} Medullary interstitial diseases, including medullar sponge kidney or nephrocalcinosis and lightchain neuropathy, are also associated with distal RTA.\textsuperscript{10} Drugs and toxins that have been associated with this distal RTA include lithium and toluene.\textsuperscript{10} Amphotericin B, a systemic antifungal medication, has been linked with increasing membrane permeability subsequently resulting in a back-leak of hydrogen ions.\textsuperscript{10} It is known that amphotericin B creates aqueous channels in lipid membranes.\textsuperscript{9} There are differing opinions and literature surrounding the exact mechanism for the leaking involved with amphotericin B–induced distal RTA.\textsuperscript{9} With this presentation, patients may be hypokalemic and will have an elevated urinary pH.\textsuperscript{9} Impairment in the cortical nephron’s sodium reabsorption may elicit a subsequent failure to secrete hydrogen ions.\textsuperscript{9} Because a decrease in sodium reabsorption is often secondary to medication use or volume depletion, this type of RTA is not generally considered a kidney disorder.\textsuperscript{9} The urinary pH is typically 5.5 or greater and may be in conjunction with hyperkalemia.\textsuperscript{9} Common conditions leading to this disorder include obstructive uropathy, triamterene or amiloride use, volume depletion, and sickle cell anemia.\textsuperscript{10} Distal RTA is also noted to be relatively common following kidney transplantation, secondary to chronic rejection.\textsuperscript{3} Clinical manifestations of the RTA syndrome type 1 include hypokalemia, hypocitraturia, hypercalcuiuria, and nephrocalcinosis.\textsuperscript{8,17} Patients may present as asymptomatic or have generalized musculoskeletal complaints including myalgia or weakness, which may progress to paralysis, often secondary to hypokalemia.\textsuperscript{7} Hyperaldosteronism-Associated RTA (Type 4) Often referred to as hyperkalemic RTA, type 4 RTA directly results from tubular resistance to aldosterone or an overall aldosterone deficiency.\textsuperscript{10} Typically, in type 4 RTA, there is a decrease in mineral corticaloid stimulation of both hydrogen ion and potassium secretion.\textsuperscript{1,10} Aldosterone is the major hormone that promotes potassium excretion; hyperkalemia is a common finding.\textsuperscript{1} While hyperkalemia persists, the nephron fails to recycle ammonia, which is associated with a presenting mild metabolic acidemia.\textsuperscript{10} Typically, the untreated urine pH is less than 5.5,\textsuperscript{10} and untreated plasma bicarbonate level is 16 to 22 mEq/L.\textsuperscript{10} Specific clinical conditions that lead to type 4 RTA are categorized by hyporeninemic hypoaldosteronism, hyperreninemic hypoaldosteronism, and aldosterone resistance (Table 2). Generally, renal insufficiency, prior to end-stage kidney disease, is associated with decreased levels of aldosterone or tubular resistance to aldosterone.\textsuperscript{1} Common causes of aldosterone resistance that can lead to type 4 RTA can be attributed to the effect of aldosterone activity on the body, either at the receptor site or via the target pathway.\textsuperscript{1} Medications that elicit this effect on the nephron include spironolactone, triamterene, amiloride, trimethoprim, and pentamidine.\textsuperscript{1,10} Hyporeninemic hypoaldosteronism can be contributed to diseases and medications including diabetes, interstitial diseases (amyloid, monoclonal gammopathies, interstitial nephritis), nonsteroidal anti-inflammatory drugs, β-blockers, and cyclosporin.\textsuperscript{1,10} The interstitial nephritis commonly seen with type 4 RTA is secondary to nonsteroidal anti-inflammatory drug use.\textsuperscript{1} Conditions associated with hypoaldosteronism without hyperreninemia include Addison disease, critical illness, and medication use including angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, heparin, and ketoconazole.\textsuperscript{1,10} **DIAGNOSTIC TESTING** There are many different diagnostic approaches for RTA. Normally, only a few of the diagnostic tests discussed are
The diagnosis of RTA is typically based on the clinical presentation, history, serum and urine results, and overall patient reaction to exogenous alkali administration.

### Serum Anion Gap

The first step in diagnosing RTA includes the calculation of the serum anion gap. The serum anion gap is calculated as:

$$\text{[Serum Anion Gap]} = ([\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-]))$$

Accounting for corrected change in serum albumin. A normal serum anion gap can be defined as 10 to 12 mEq/L. An elevation in the serum anion gap (>12) is typically associated with ketoacidosis, lactic acidosis, or intoxication of salicylate, methanol, or ethylene glycol. If the serum anion gap is normal (<12), the practitioner must consider the differential diagnoses of a non-anion gap metabolic acidosis. Common differential diagnoses for a non-anion gap metabolic acidosis include bicarbonate wasting secondary to diarrhea, GI fistula, ureterosigmoidostomy, RTA, renal insufficiency, acetazolamide use, large-volume saline resuscitation, and urine-gut diversions. The practitioner should bear in mind that a presentation of unexplained non-anion gap metabolic acidosis warrants consideration of abnormal tubular function.

### Urinary pH

A second test used in the diagnosis of RTA is the measurement of the urinary pH. Essentially, by obtaining and evaluating the urinary pH, the practitioner is examining the overall integrity of mechanisms involved in distal urinary acidification. However, the urinary pH does not measure the total hydrogen ion excretion, as it is a measurement of the free hydrogen ions, which account for less than 1% of all excreted protons. Although the urine dipstick pH measurement is known to be relatively inexpensive and widely available, it has also been shown to be unreliable. For increased sensitivity, a fresh morning random urine sample should be obtained and measured via the pH electrode. Typically, the utilization of urinary pH is associated with diagnosing type 1 RTA after the practitioner has excluded conditions that may result in an inappropriately high (>5.5) urinary pH associated with metabolic acidosis. These conditions include UTIs with urea-splitting organisms, hypokalemia.
(may be severe), and salt retention secondary to GI loss or inadequate intake.\textsuperscript{2,9} While the sensitivity for the diagnosis of all forms of RTA with the urinary pH is poor, a urinary pH evaluated as low (<5.5)\textsuperscript{9} is typically depicted in types 2 and 4 RTA.

**Urine Acidification Testing**

First outlined by Wrong and Davies\textsuperscript{19} in 1959, the classic approach to urine acidification testing included the ammonium chloride loading test. The main purpose of this test is to evaluate for type 1 RTA in the presence of a mild systemic acidosis that may otherwise go undetected.\textsuperscript{4,9} The test is composed of administering 0.1 g of ammonium chloride per kilogram orally and subsequently measuring the urinary pH multiple times up to 6 to 8 hours following administration.\textsuperscript{9,12} By administering ammonium chloride, the practitioner is working to create an environment that allows the kidneys to excrete hydrogen ions maintaining a normal range of serum; urine pH provides confirmatory information.\textsuperscript{2} In response to the administration of the ammonium chloride, a relatively healthy individual will obtain a urinary pH of less than 5.3,\textsuperscript{9} whereas the inability to reach a urinary pH of this value is significant for the diagnosis of type 1 RTA.\textsuperscript{7} With types 2 and 4 RTA, the urinary pH will fall below 5.5.\textsuperscript{9}

An alternative test that is used in the situation of an individual who is unable to develop metabolic acidosis during the short test discussed above is a 3-day ammonium chloride test.\textsuperscript{9} Similar to the shorter version, the dose of ammonium chloride is administered on 3 consecutive days, and a urinary pH measurement is obtained on the third day.\textsuperscript{9} This test can also be useful in the measurement of NH\textsubscript{4}\textsuperscript{+} arrangement, which may take up to 72 hours to complete.\textsuperscript{9} However, because this test must be performed over a 3-day period, it can be difficult to complete for many patients.\textsuperscript{12} In the presence of liver failure, literature suggests the administration of oral calcium chloride and intravenous arginine hydrochloride in place of the ammonium chloride, although neither is commonly used in practice.\textsuperscript{9}

**Sodium Sulfate or Furosemide Challenge**

Another approach to diagnostic testing with RTA includes the administration of furosemide or sodium sulfate. The presenting sodium levels must be evaluated, as this test requires a salt-deficient state through sodium restriction or furocortisone administration.\textsuperscript{9} With the administration of the sodium sulfate or furosemide, there is an increase in distal sodium delivery, subsequently resulting in a transepithelial voltage difference that is negative secondary to sodium reabsorption. A high filtrate sodium load and subsequent change in cellular transmembrane voltage promote hydrogen and potassium loss from serum into filtrate.\textsuperscript{4,9,20} Normal results confirming RTA would be a urinary pH\textsuperscript{9} less than 5.5 and a concurrent increase in net acid and potassium excretion.\textsuperscript{4,9} The use of furosemide is increasingly popular for individuals presenting with type 4 RTA, as acid loading is contraindicated with hyperkalemia.\textsuperscript{4} However, because the consistency of this test depends on relative sodium depletion, the test’s use may be limited.

**Bicarbonate Administration and Urine PCO\textsubscript{2}**

The administration of bicarbonate as a test in diagnosing RTA surrounds the idea that hydrogen ions that are distally secreted will bind to bicarbonate and subsequently form carbonic acid and dehydrates to carbon dioxide.\textsuperscript{9} Therefore, there is an increase in urine PCO\textsubscript{2} with normal functioning of the distal proton pump.\textsuperscript{9,18} A typical urine to serum PCO\textsubscript{2} level is defined as greater than 3.3 to 4.0 kPa.\textsuperscript{9} While monitoring the urinary pH during bicarbonate administration, if the urinary pH reveals alkalinosis prior to the serum bicarbonate level and then equilibrating to normal, the patient is said to have a decreased ability to reabsorb bicarbonate.\textsuperscript{18} This is congruent with the diagnosis of type 2 RTA. However, if the opposite occurs, and the serum HCO\textsubscript{3}~ normalizes prior to the alkalinization of the urinary pH, the patient is thought to have a normal ability to reabsorb HCO\textsubscript{3}~, which rules out the diagnosis of type 2 RTA.\textsuperscript{18} While a small amount of HCO\textsubscript{3}~ wasting occurs in type 1 RTA, it is noted that bicarbonate excretion fails to surpass 10% of the total filtered HCO\textsubscript{3}~ load.\textsuperscript{18}

## Diagnosis

Initially, a diagnostic approach for RTA should include awareness for the typical presenting characteristics and patients at risk for development of RTA. The first step in the diagnosis of RTA should include confirming the diagnosis of metabolic acidosis, which is defined as having a low serum bicarbonate and a negative base excess.\textsuperscript{12} Following the diagnosis of metabolic acidosis, a serum anion gap should be calculated. Once the diagnosis of non-anion gap metabolic acidosis is reached, a urine anion gap can be calculated, as this further differentiates between RTA and other possible causes of acidosis. As discussed above, the urinary anion gap is a reliable indicator of ammonium excretion and is a relatively quick way to differentiate between types 1 and 2 RTA.\textsuperscript{9} If the urinary anion gap is negative, considerations of GI bicarbonate loss, acetazolamide use, unmeasured ions, and type 2 RTA should be evaluated. To determine a proximal bicarbonate loss with a negative urinary anion gap, a fractional excretion of bicarbonate should be evaluated during exogenous bicarbonate administration.\textsuperscript{9} Only in type 1 RTA, an administration of 2 to 5 mmol per kilogram of

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alkali will result in a correction of acidosis. Typically, type 2 RTA is diagnosed by exclusion or by nonresponse to an alkali test dose.

In the presence of a positive urinary anion gap, practitioners must consider distal defects in urinary acidification. The urinary pH may be measured following an acid load, as the inability to decrease the urinary pH less than 5.5 indicates a diagnosis of distal RTA. As previously mentioned, it is imperative to evaluate for UTIs, hypokalemia, and volume losses prior to diagnosing a distal RTA, as these conditions may result in an increased urinary pH (>5.5). With a presenting increased serum potassium and urinary pH greater than 5.5, a diagnosis of hyperkalemic distal RTA may be secondary to a voltage defect. However, if the presentation includes hyperkalemia with a low urinary pH, type 4 RTA should be considered secondary to a deficiency or resistance to aldosterone. A serum aldosterone level may be obtained to further examine the cause of the presenting RTA.

Although there are many different diagnostic tests that may be performed to evaluate for the presence of RTA, it is increasingly common to use only 1 or 2 of the diagnostic tests discussed along with a thorough review of presenting clinical findings and medications. The algorithm in Figure offers an overall diagnostic approach to the diagnosis of RTA.

![Figure. Algorithm for the diagnostic approach for renal tubular acidosis.](image_url)
**TREATMENT**

The common approach to treatment of RTA includes alkali replacement therapy and reversal of the causative process or agent. In type 2 RTA, typically large amounts of alkali are necessary to reverse the presenting metabolic acidosis. While oral sodium bicarbonate and potassium citrate may be used, many individuals prefer to use the potassium citrate to avoid the adverse GI effects associated with oral sodium bicarbonate. Practitioners can also prescribe thiazide diuretics to promote proximal tubule HCO$_3^-$ reabsorption. As discussed previously, type 2 RTA is commonly associated with Fanconi syndrome, which may necessitate the addition of calcium, phosphate, or vitamin D as well. Serum potassium levels must also be closely monitored during treatment, as already low serum potassium levels may rapidly decline with the correction of metabolic acidemia.

With type 1 RTA, therapy should be aimed toward correcting the underlying disorder. Also, the metabolic acidosis may be corrected through the use of oral bicarbonate replacement with 1 to 2 mEq/kg per day with sodium bicarbonate or sodium citrate. In presentations of hypokalemia with type 1 RTA, it may be necessary to include potassium citrate in the treatment plan. Treatment for type 4 RTA includes correction of the presenting hypokalemia through a dietary restriction of potassium of 40 to 60 mEq/day along with a loop diuretic. It may also be beneficial to add 0.5 to 1 mEq/kg per day of oral sodium bicarbonate. If primary adrenal insufficiency is diagnosed, mineral corticoid administration should be considered.

In the presence of both distal and proximal RTA, the risk for osteomalacia is increased secondary to mobilization of calcium. The mobilization of calcium can be attributed to bone metabolism. With type 2 RTA, calcium loss and subsequent bone loss are a result of phosphate wasting and decreased vitamin D metabolism. There is an increased risk with type 1 RTA for nephrocalcinosis and nephrolithiasis, leading to renal colic, urinary tract obstruction, and UTIs. Long-term follow-up is recommended for patients who experience RTA to monitor for bone and kidney complications.

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**CONCLUSION**

The 3 forms of RTA are secondary to a variety of inherited and acquired disorders. Renal tubular acidosis can further result in a multitude of complications that may present as acute or chronic. In the presence of a non-anion gap metabolic acidosis, practitioners should always consider a tubular disorder and include RTA on the list of differential diagnoses. Although a relatively uncommon disorder, prompt diagnosis and intervention can prevent complications and reverse renal dysfunction.

**References**


**ABOUT THE AUTHOR**

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