



Renal Tubular Acidosis

Laura Riordan, DVM

Michael Schaer, DVM, DACVIM, DACVECC

University of Florida

ABSTRACT:

This article discusses the pathophysiology, causes, diagnosis, treatment, and prognosis of renal tubular acidosis (RTA) in veterinary patients. RTA is classified as a non-anion-gap metabolic acidosis in the presence of a normal glomerular filtration rate. Proximal RTA occurs because of a deficiency in bicarbonate resorption in the proximal tubule, whereas distal RTA occurs because of decreased production of bicarbonate in the distal tubule. RTA can be transient or permanent and can occur secondary to other diseases. Therapy includes bicarbonate supplementation with careful acid–base and electrolyte monitoring and treatment of underlying causes.

There are few published discussions of renal tubular acidosis (RTA) in the veterinary literature despite the abundance of reports of such disorders in humans. Although it is possible that the incidence of such conditions in small animals is less than that in humans, it is also plausible that tubular disorders are overlooked in veterinary patients (Table 1).

RTA typically causes metabolic acidosis with both a normal anion gap and normal glomerular filtration rate (GFR). In contrast, renal failure is often associated with an increased anion gap due to the presence of phosphates, sulfates, and organic anions as well as a reduced GFR. Traditionally, RTA has been classified into four types in human medicine: type 1 (i.e., distal tubular acidosis), type 2 (i.e., proximal tubular acidosis), type 3 (i.e., an ill-defined combination of proximal and distal tubular acidosis), and type 4 (i.e., hyperkalemic RTA). Type 3 RTA is an obsolete term because it is no longer considered a distinct form of RTA. Type 4 RTA is associated with hyperkalemia and decreased renin and aldosterone concentrations. In hu-

mans, this is most commonly recognized in patients with concurrent diabetes mellitus and renal insufficiency.¹ Types 3 and 4 have not been reported in the veterinary literature and are not discussed in depth in this article. Because of the anatomic relationship of the tubules, numeric assignments for the varying forms of RTA can be confusing. Therefore, numeric descriptions of the various types of RTA are avoided in this article.

RENAL PHYSIOLOGY

RTA cannot be adequately understood without a good foundation in renal physiology. The proximal and distal tubules play key roles in regulating plasma bicarbonate, thus strongly affecting acid–base balance (Figure 1). The proximal tubule resorbs bicarbonate ions present in the glomerular filtrate, thereby preventing their loss in the urine. The distal tubule is responsible for producing bicarbonate, which replaces that used in buffering the daily acid load.

THE PROXIMAL TUBULE

The flow of urine through the proximal tubule greatly alters the composition of glomerular filtrate. Approximately 80% of filtered

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Table 1. Expected Biochemical and Clinical Findings in Dogs with Renal Tubular Acidosis^{3,11,12,26}

	Proximal RTA	Distal RTA
Serum bicarbonate	15–18 mEq/L	≤10–12 mEq/L
Serum phosphorus	Low or normal	Low or normal
Serum potassium	Low or normal	Voltage dependent: High Classic: Low Leaky membrane: Low
Urine glucose	Frequently present	Absent
Urine amino acids	Frequently present	Absent
Urine phosphate	Increased	Increased
Urine calcium	Increased	Increased
Urine citrate	Normal	Decreased
Urine pH during acidosis	<6	>6
Bicarbonate required for treatment	>10 mEq/kg/day	<3 mEq/kg/day
Bone disease	Rare	Common
Nephrolithiasis or nephrocalcinosis	Rare	Common

bicarbonate and about 65% of filtered sodium and water are reabsorbed in the proximal tubule.^{2,3} In addition, nearly all filtered glucose, phosphate, and amino acids are reclaimed at this site.

The proximal tubule cell maintains a low intracellular concentration of sodium through the action of a sodium ion (Na⁺)/potassium ion (K⁺)-ATPase pump on the basolateral membrane (Figure 2). In exchange for potassium, the proximal tubule cell pumps out sodium through an active process driven by hydrolysis of ATP. Thus a gradient is established between the tubular lumen and proximal tubule cell so that sodium can passively diffuse into the tubule cell down its concentration gradient. This movement of sodium also provides energy for transporting glucose, phosphate, and amino acids into the tubule cell, effectively reabsorbing nearly all that was filtered by the glomerulus.

Sodium reabsorption also facilitates the active exchange of sodium and hydrogen between the proximal tubule cell and lumen (Figure 3). The hydrogen is derived from intracellular conversion of water to hydrogen ion (H⁺) and hydroxide (OH⁻). The secreted hydro-

gen binds to bicarbonate in the filtrate to form carbonic acid (H₂CO₃), which rapidly dissociates to form carbon dioxide (CO₂) and water. CO₂ then diffuses back into the proximal tubule cell, where, catalyzed by carbonic anhydrase, it combines with the previously formed OH⁻ to form H₂CO₃. Within the tubular cell, this H₂CO₃ dissociates into bicarbonate and H⁺, the latter of which is pumped back into the tubular lumen in exchange for sodium. By passive diffusion down an electrical gradient, bicarbonate passes into the plasma from the proximal tubule cell and effectively maintains the acid–base balance in the blood.

Bicarbonate absorption is an indirect process. The bicarbonate in glomerular filtrate must combine with secreted H⁺ to diffuse into the proximal tubule cell as CO₂ and be converted back into bicarbonate intracellularly. Therefore, it is important to recognize that bicarbonate reabsorption has the same functional effect as H⁺ secretion into the proximal tubule lumen.⁴

THE DISTAL TUBULE

Despite the nearly complete reabsorption of filtered bicarbonate in the proximal tubule, there would be a marked deficit in plasma bicarbonate concentration without its production by the distal tubule. This need for bicarbonate synthesis is due to the use of bicarbonate in buffering the daily acid load. The metabolism of dietary proteins and catabolism of dietary lipids result in production of sulfuric acid and phosphoric acid. An estimated acid load of 50 to 100 mmol/day leads to 50 to 100 mEq of hydrogen ion that requires buffering by bicarbonate each day.² To maintain acid–base homeostasis, bicarbonate must be synthesized to compensate for its tremendous consumption. For simplicity's sake, the synthesis of bicarbonate can be divided into three steps:

- Sodium reabsorption by the distal tubule principal cells
- H⁺ secretion by the intercalated cells of the distal tubule
- Prevention of back diffusion of hydrogen ions into the distal tubule cells by an impermeable distal tubular wall

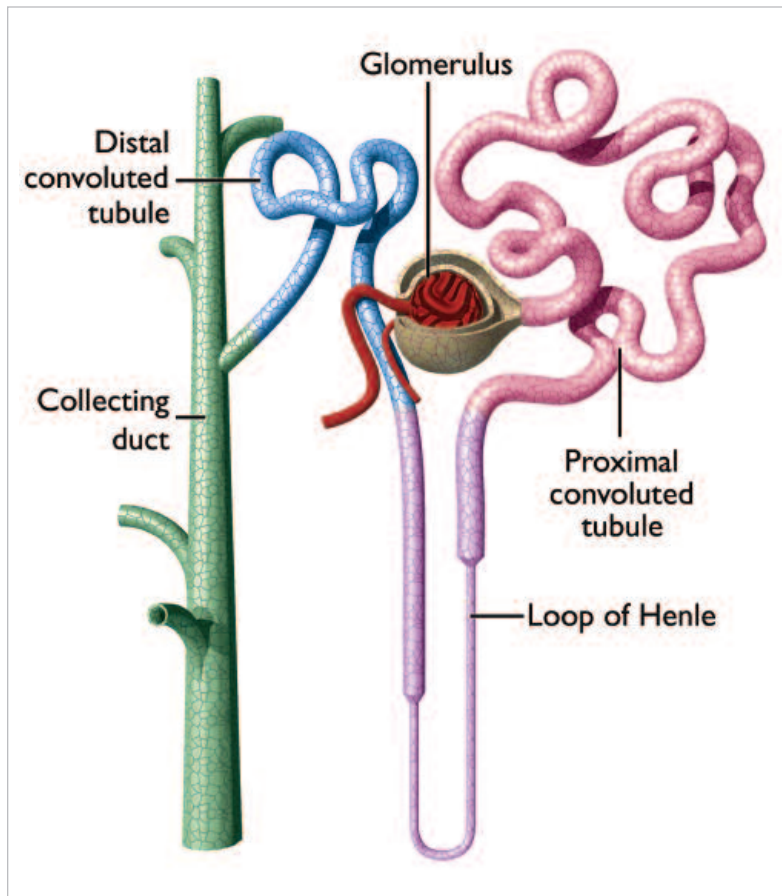


Figure 1. The proximal and distal tubules of the nephron play key roles in regulating plasma bicarbonate and, subsequently, the acid–base balance. (Illustration by Felicia Paras)

Sodium passively diffuses into the principal cell of the distal tubule, thereby establishing an electrical gradient between the intracellular and tubular environments (Figure 4). The negative charge in the tubular lumen aids in H^+ secretion by the distal tubule intercalated cells. The dissociation of water inside the intercalated cell allows formation of H^+ and OH^- . Hydrogen is actively secreted into the tubular lumen by an H^+ -ATPase pump. The OH^- combines with CO_2 intracellularly to form new bicarbonate that diffuses into the bloodstream. The concentration of H^+ within the tubular lumen is significantly higher than that in the distal tubule cells. Therefore, the tubule wall must be impermeable to H^+ to prevent the passive diffusion of the ion down its concentration gradient back into the tubular cells.

The excretion of hydrogen ions secreted into the distal tubule occurs in three forms: ammonium ion (NH_4^+), titratable acids (HPO_4^- , dihydrogen phosphate anion),

and free H^+ . Most of the hydrogen ions combine with ammonia (NH_3) to be excreted as NH_4^+ . The ammonia is produced by glutamine in the tubular cells in proportion to the daily acid load, where more ammonia is produced and more ammonium excreted in the presence of an increased acid load. Anions filtered by the glomerulus also combine with hydrogen to form titratable acids. Because the amount of anions filtered by the glomerulus is unchanged regardless of the daily acid load, the amount of hydrogen excreted in the form of titratable acids is constant, leaving only a small amount of hydrogen to be excreted in the free ion form.

PROXIMAL RTA Pathophysiology and Bicarbonate Handling

Proximal RTA is characterized by reduced bicarbonate reabsorption in the proximal tubule. As with other solutes, there is a maximum rate for bicarbonate reabsorption known as the *transport maximum* (T_m). This value describes the maximum plasma bicarbonate concentration at which all of the bicarbonate present in the filtrate will be reabsorbed. At concentrations greater than this T_m , excess bicarbonate will be lost in the urine. The normal T_m for bicarbonate in dogs is 24 to 26 mEq/L.³ Hence, in a normal dog, bicarbonate is not lost in the urine until the plasma bicarbonate concentration exceeds 26 mEq/L. In a dog with proximal RTA, however, the T_m for bicarbonate is reduced (i.e., usually 12 to 20 mEq/L).⁵ Essentially, this translates into urinary loss of bicarbonate at lower plasma bicarbonate concentrations compared with those in normal animals.

Fortunately, bicarbonate loss is limited by the T_m for bicarbonate. Once the plasma bicarbonate level equals the T_m , a new steady state is achieved in which the amount of bicarbonate filtered by the glomerulus equals the reabsorptive capacity of the tubule⁵ (Figure 5). Thus in the steady state, as long as distal tubular function is normal, bicarbonate reabsorption and production occur normally. Therefore, H^+ is excreted in the urine, producing acidic urine that is appropriate in the presence of metabolic acidosis.

When the patient's plasma bicarbonate is above the T_m , a smaller percentage of bicarbonate is reabsorbed, leading to loss of bicarbonate in the urine. In this scenario, the urine is alkaline despite the presence of meta-

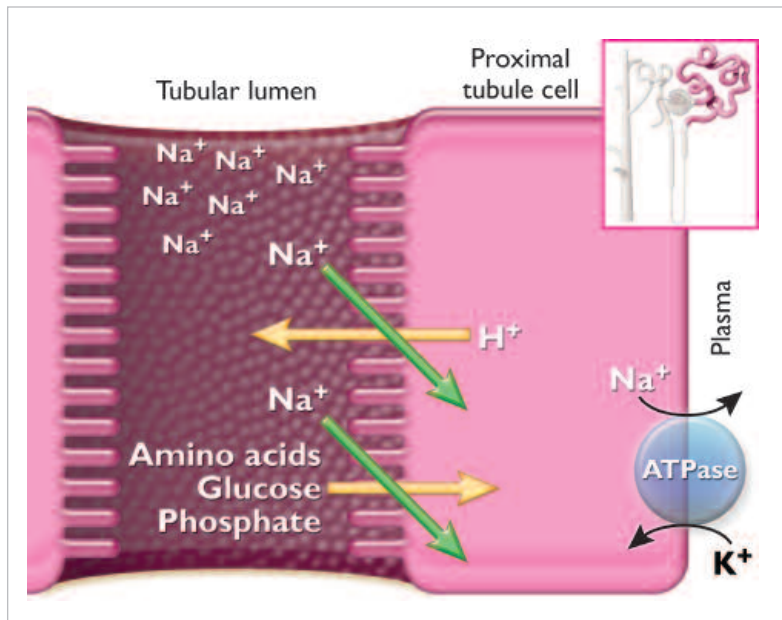


Figure 2. Proximal tubule cells maintain a low intracellular Na^+ concentration via a Na^+/K^+ -ATPase pump. Subsequent flow of Na^+ down its concentration gradient into the cells provides the energy for reabsorption of glucose, phosphate, and amino acids as well as secretion of H^+ . (Illustration by Felicia Paras)

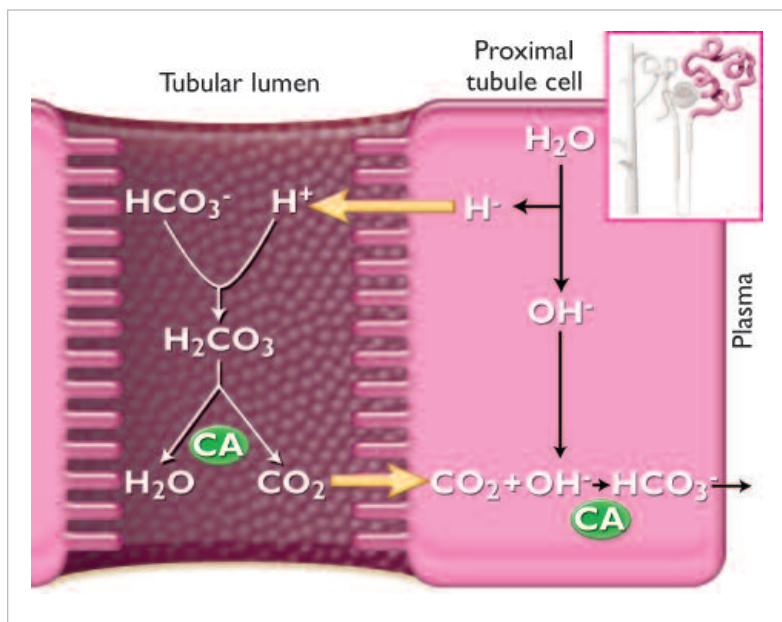


Figure 3. Sodium reabsorption (Figure 2) facilitates the active exchange of sodium and hydrogen. Intracellular water converts to H^+ and OH^- . Secreted H^+ binds to bicarbonate in the lumen to form H_2CO_3 that dissociates to CO_2 and water. CO_2 diffuses back into the cell and combines with OH^- via carbonic anhydrase to form H_2CO_3 . This dissociates into H^+ and bicarbonate, which passively diffuses into the plasma to maintain the acid-base balance. (Illustration by Felicia Paras)

bolic acidosis. This may be seen in animals early in the disease process before a steady state has been reached. Conversely, if a patient's plasma bicarbonate concentration is less than the T_m , the proximal tubule is capable of reabsorbing all of the bicarbonate in the glomerular filtrate. However, distal tubule production of bicarbonate is necessary to increase the plasma bicarbonate to the steady state concentration. Bicarbonate production in the distal tubule is associated with secretion of H^+ and subsequent acidification of urine.

Hypokalemia

In addition to bicarbonate loss, proximal RTA may be associated with potassium wasting for two reasons. For one, increased bicarbonate in the proximal tubule creates an electronegative luminal environment that promotes potassium secretion. In addition, just as the reabsorption of bicarbonate and sodium in the proximal tubule is linked, so too is the loss of K^+ . With increased loss of bicarbonate and sodium, there is a proportional increase in water loss. This increased luminal water translates to higher flow through the distal tubule. The secreted potassium in the distal tubule lumen is quickly flushed away because of the higher flow, thereby reestablishing a concentration gradient that favors further potassium secretion. Aldosterone secretion is also stimulated by hypovolemia associated with increased water loss. The action of aldosterone mediates the continued loss of potassium via its action on the distal tubule.

Despite the physiologic tendency for hypokalemia, most humans have normal serum potassium levels at the time of diagnosis. In theory, potassium wasting could be potentiated with alkali therapy. Increased delivery of sodium bicarbonate to the distal tubule would seem to increase the exchange of sodium and potassium and subsequently increase urinary potassium. However, this does not seem to be the case in many humans.⁶ However, in dogs with Fanconi syndrome, which includes proximal RTA among other proximal tubule defects, hypokalemia can develop in the later stages of the disease.⁷

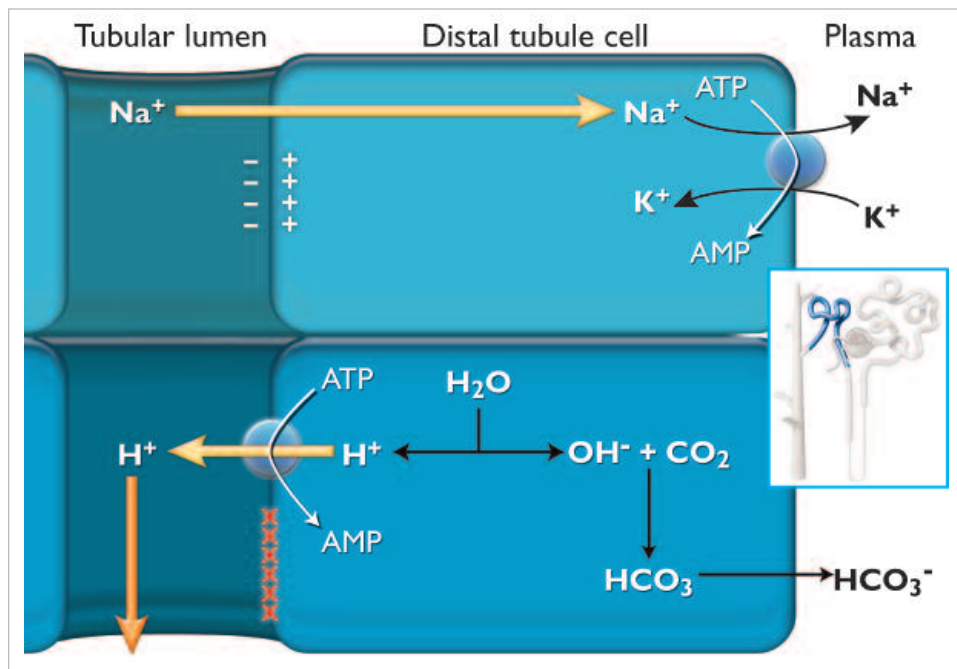


Figure 4. Passive diffusion of sodium into the principal cell creates a negative charge in the lumen, which aids intercalated cells in H^+ excretion via an H^+ -ATPase pump. The tubular wall is impermeable to H^+ , thereby preventing its passive diffusion back into the cells. The dissociation of water within the intercalated cell creates H^+ (which is pumped into the lumen) and OH^- . OH^- combines with CO_2 to form bicarbonate, which diffuses into the plasma. (Illustration by Felicia Paras)

Complications

The major complication of proximal RTA in humans is bone destruction related in part to chronic metabolic acidosis. To buffer hydrogen, both bicarbonate and phosphate are released from bone. This bony destruction is enhanced by an acquired vitamin D deficiency that develops because of failure of the proximal tubule to convert vitamin 25-OH-D to vitamin 1,25-(OH)₂-D. The latter is responsible for raising or sustaining plasma calcium concentrations by increasing calcium absorption from the intestine and calcium reabsorption from bone. Subsequent development of hypocalcemia from vitamin D deficiency leads to increased production of parathyroid hormone. In the hyperparathyroid state, both calcium and phosphate are released from the already compromised bone. Because acidemia is mild in the steady state of proximal RTA, bone disease such as rickets or osteomalacia is considerably less likely to occur compared with patients with distal RTA. Reports of proximal RTA in the veterinary literature suggest that this bone pathology occurs only rarely in dogs. In a case report of two border terriers with renal dysplasia and

Fanconi syndrome, histologic evidence of rickets was found and resolved with calcitriol and potassium phosphate therapy.⁸

Unlike patients with distal RTA, patients with proximal RTA are also at little risk of nephrolithiasis. The solubility of calcium is increased by both acidification of the urine by the distal tubule and higher concentrations of citrate and amino acids in the filtrate.

Fanconi Syndrome

Fanconi syndrome in dogs is characterized by impairment of renal tubular reabsorption of several molecules and ions, including amino acids, glucose, sodium, potassium, calcium, phosphate, bicarbonate, and uric acid. The condition can be congenital, as in basenjis, or acquired as a result of proximal tubule insult. The congenital form has

been well described in basenjis, along with isolated reports in other breeds.^{9–11} In basenjis, the disorder is postulated to be due to a defect in either sodium transport or amino acid leakage back into the tubular lumen.¹² Patients with Fanconi syndrome often have substantial polyuria and polydipsia. Weight loss in these patients has been associated with chronic, persistent acidosis rather than urinary loss of amino acids.¹³ These patients are more predisposed to bone density loss and bone pain than those with isolated proximal RTA. Hypophosphatemia resulting from excessive urinary phosphate loss and hypercalciuria are the primary causes of such bone pathology. As in patients with isolated RTA, hypokalemia can cause muscle weakness.

Causes

Several causes of acquired proximal RTA, many of which could lead to the disorder in small animals, have been reported in humans. The presence of proximal RTA without other signs of proximal tubule dysfunction is rare. Urinary loss of glucose, uric acid, phosphate, and/or amino acids is often noted in conjunction with

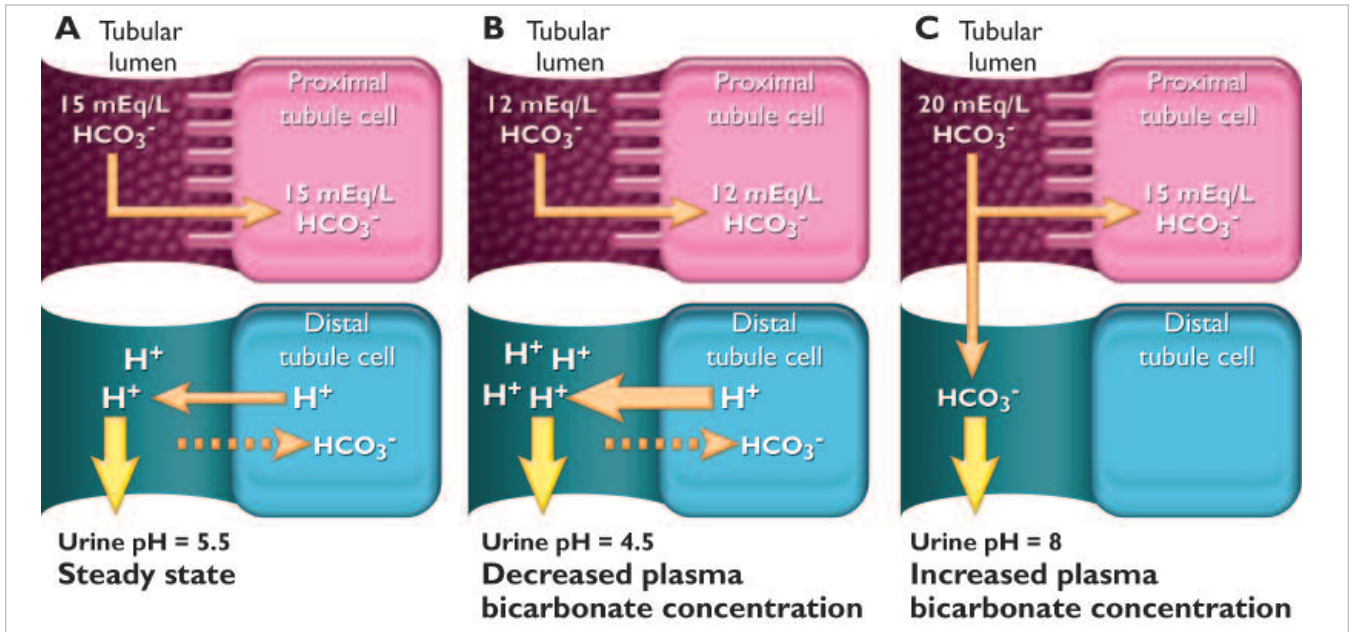


Figure 5. In steady-state proximal RTA, the plasma HCO_3^- is equal to the T_m of HCO_3^- in the proximal tubule. Because the distal tubule continues to produce and reabsorb HCO_3^- , the urine is acidic. When plasma HCO_3^- is less than T_m , the distal tubule increases bicarbonate production (increases H^+ secretion) to bring the plasma HCO_3^- back to the steady state. When plasma HCO_3^- is greater than T_m , bicarbonate is lost in the urine, creating alkaline urine. (Illustration by Felicia Paras)

bicarbonate loss due to generalized damage or defects in the proximal tubule.

Although the congenital form predominates in dogs, Fanconi syndrome has reportedly occurred secondary to drug administration and other disease processes. Experimental administration of maleic acid to dogs resulted in Fanconi syndrome.¹⁴ Because gentamicin first disrupts cellular transport mechanisms, proteinuria, aminoaciduria, and glycosuria may be the first signs of gentamicin nephrotoxicity.^{15,16} Thus although continued gentamicin administration can result in a declined GFR, azotemia is preceded by Fanconi syndrome. Acquired Fanconi syndrome in dogs has also been reported in association with suspected ethylene glycol toxicosis.¹⁷

Although there are several reported causes of proximal RTA in humans, much of the pathophysiology remains to be described. Some drugs, such as the chemotherapeutic drug ifosfamide, are directly toxic to the proximal tubule. Cisplatin, streptozotocin, and expired tetracycline have also been associated with proximal tubule damage and subsequent RTA in humans.¹⁸ Streptozotocin, a chemotherapeutic that has been used with limited success in treating canine insulinomas, causes proximal tubular cell necrosis. Renal toxicity is dose-related and cumulative.¹⁹ Dogs receiving intravenous streptozotocin devel-

oped euglycemic glucosuria and decreased inorganic phosphate clearance; however, the presence of RTA was not investigated.²⁰ Under the influence of heat, moisture, and low pH, tetracycline degrades into several by-products. One such metabolite, 4-epianhydrotetracycline, has been identified as toxic to the renal tubules.²¹ Tubular cells undergo hydropic degeneration, which is more pronounced in the proximal tubules than the distal tubules.²² Acetazolamide, a diuretic used to treat glaucoma, can also cause proximal RTA by inhibiting carbonic anhydrase, the intracellular enzyme that facilitates bicarbonate resorption. Fortunately, the tubular defect normalizes once the drug is withheld.

Many heavy metals are also directly toxic to the renal tubule: Exposure to lead, mercury, and cadmium can all disrupt proximal tubule transport. Hypocalcemic conditions such as hypoparathyroidism, vitamin D deficiency, and chronic renal failure can also lead to proximal RTA. Transient Fanconi syndrome was reported in a dog with hypoparathyroidism.²³ This dog was also deficient in 1,25-dihydroxycholecalciferol and, because vitamin D deficiency reportedly causes reversible Fanconi syndrome in humans, this deficiency may have caused the transient tubular defects.⁶ In addition, there are numerous reports of proximal RTA associated with multiple

myeloma in humans thought to be due to the renal toxicity of light chains.²⁴

Although leptospirosis has not been described as a cause of proximal RTA in dogs, a human with leptospirosis also reportedly had reversible proximal tubular dysfunction in the absence of renal failure.²⁵ Hypokalemia, hypophosphatemia, and hypouricemia were noted in conjunction with inappropriate excretion of potassium, phosphate, and uric acid. In addition, renal glycosuria was diagnosed with increased urinary glucose excretion in the presence of normoglycemia. These abnormalities resolved following treatment with penicillin. Although the patient was not acidotic, the severity of proximal tubular damage suggests that leptospirosis may be a potential cause of proximal RTA in both humans and animals. Further support comes from experimental *Leptospira* spp infection of guinea pigs and fractional urinary clearance studies showing that decreases in proximal tubule sodium and bicarbonate absorption occur as a result of proximal RTA.²⁶

Diagnosis

Proximal RTA is often more difficult to diagnose than is distal RTA because patients with proximal RTA lack many clinical signs and have the ability to acidify urine once in the steady state. Patients with proximal RTA in the steady state characteristically have acidic urine with a urinary pH of usually 5.5 to 6, along with hyperchloremic metabolic acidosis. This form of acidosis is characterized by increased bicarbonate loss rather than increased H⁺ production. If the anion gap is calculated as $(\text{Na}^+ + \text{K}^+) - (\text{chloride anion } [\text{Cl}^-] + \text{bicarbonate anion } [\text{HCO}_3^-])$, the value should be in the normal range (i.e., 12 to 25 mEq/L).¹² To maintain a normal anion gap despite a reduced plasma bicarbonate concentration, the plasma chloride concentration increases. Hence, RTA is characterized as a hyperchloremic, non-anion-gap metabolic acidosis. By definition, these described changes occur in the presence of normal GFR. If these findings are present, a bicarbonate challenge can be conducted to determine whether the patient has proximal RTA. Bicarbonate is administered via constant-rate infusion so that the serum bicarbonate concentration increases to 0.5 to 1 mEq/L/hr.²⁷ In patients with proximal RTA, the urine pH increases to greater than 6 and the urinary fractional excretion of bicarbonate increases to greater than 15% once the serum bicarbonate level is in the normal range.²⁷ Because this diagnostic procedure is not readily available

for most clinicians, response to empirical therapy with bicarbonate, as will be discussed, can serve as a means of clinical diagnosis of the condition.

As previously indicated, proximal RTA rarely occurs independently from other proximal tubular abnormalities. Thus the discovery of glycosuria in a normoglycemic patient may warrant investigation into other proximal tubular abnormalities besides reduced tubular glucose resorption. Along with an evaluation for proximal RTA, fractional urinary excretion of electrolytes and amino acids can be measured by collecting a 24-hour sample of urine. Samples can be sent to the Metabolic Genetic Disease Testing Laboratory of the School of Veterinary Medicine at the University of Pennsylvania (PennGen) to screen for amino and lactic aciduria.

Treatment

Treatment of both proximal RTA and Fanconi syndrome is aimed at reducing the plasma bicarbonate deficit. As bicarbonate is supplemented, the steady state is lost. The plasma bicarbonate rises above the T_m, allowing bicarbonate loss in the urine. To correct acidosis, it is necessary to supplement enough bicarbonate to keep up with the renal loss. Unfortunately, the large amounts of sodium bicarbonate required to normalize both the pH and serum bicarbonate can aggravate potassium wasting. Therefore, alkali treatment can require concurrent therapy with potassium gluconate.^{4,10} Because of the presence of hyperchloremic metabolic acidosis, potassium chloride should be avoided. Because the plasma potassium concentration fails to reflect total body potassium, it can be difficult to accurately determine the potassium deficit. A total daily dose of 1 mEq/kg can be given initially in divided doses.¹⁰ Patients with proximal RTA may require over 10 mEq/kg/day of bicarbonate to correct serum bicarbonate and pH disturbances.^{28–30} Electrolytes should be monitored closely, especially until the plasma pH and bicarbonate normalize. The greater the required dose of bicarbonate, the greater the potential is for significant hypokalemia. Potassium gluconate elixir can be used in patients with hypokalemia or in those that develop hypokalemia with alkali therapy. A dose of 1 mEq/kg/day PO can be given in divided doses.¹³ In addition, the reported adverse effects of bicarbonate therapy in humans include metabolic alkalosis, abdominal bloating, and increased intestinal gas production.³¹ These effects have not been reported in small animals; however, they may occur. Potassium citrate may be a better option for long-term alkali treatment.¹² In addition to correcting acidosis, potassium

citrate also provides a source of potassium that may be needed if a patient is hypokalemic. The recommended dose in humans with proximal RTA is 3 to 4 mEq/kg/day. Although doses for treating small animals with RTA have not been published, a published dose of potassium citrate for preventing calcium oxalate crystal formation in dogs with hypocitraturia is 150 mg/kg/day (approximately 1.35 mEq/kg/day) divided into two doses.³² This serves as a reasonable initial dose for dogs with proximal RTA, with subsequent titration aimed at normalizing potassium and reducing the severity of acidosis.

A comparatively aggressive form of bicarbonate treatment has been established for dogs with idiopathic Fanconi syndrome and is included in the Gonto protocol.³³ In this regimen, dogs are also supplemented with vitamins, amino acids, and minerals. The details of this protocol are published elsewhere, and its efficacy compared with other treatment protocols remains to be established.³³

Administering hydrochlorothiazide to treat proximal RTA has had variable results in humans.³⁴ Hydrochlorothiazide would be expected to increase bicarbonate resorption in the proximal tubule by mildly contracting the plasma volume.^{6,34} Although the drug has been effective in correcting acidosis in some patients, in others, acidosis persisted and therapy induced severe hypokalemia. Because some studies have found that high doses of bicarbonate can decrease the reabsorptive capacity of the proximal tubule by lowering the T_m , hydrochlorothiazide therapy could be considered in cases requiring exceedingly high doses of bicarbonate to correct plasma bicarbonate.³⁵ A starting dose of 1.5 to 2 mg/kg/day is recommended in humans, and the dose should be lowered when acidosis has been corrected. Potassium supplementation is initiated concurrently to avoid hypokalemia, which can be exacerbated with diuretic therapy.³⁶ Because there are no reports of such

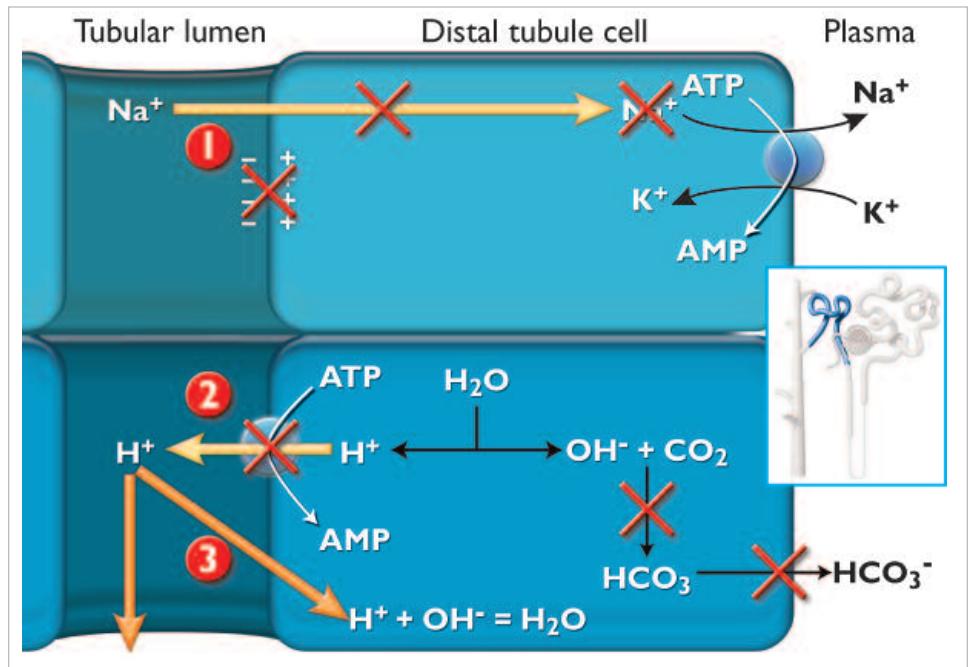


Figure 6. Causes of distal RTA. All three of these mechanisms can prevent HCO_3^- production and reabsorption in the distal tubule. (Illustration by Felicia Paras)

- 1 Voltage dependence:** Loss of Na^+ reabsorption prevents formation of a negative charge in the tubule.
- 2 Impaired H^+ -ATPase pump:** Failure of the H^+ pump prevents secretion of H^+ .
- 3 Increased tubule membrane permeability:** The leaky tubule membrane allows H^+ backflow and formation of water.

diuretic therapy in dogs or cats with proximal RTA, it is unclear whether this treatment would be beneficial.

During initial alkali therapy, electrolyte concentrations should be monitored every 1 to 2 weeks. Venous blood gases can be monitored similarly to evaluate bicarbonate concentration and pH. Once these values have stabilized, quarterly rechecks should be sufficient in monitoring electrolytes, bicarbonate, and pH. Urine specific gravity, serum creatinine, and blood urea nitrogen should be evaluated for evidence of renal failure, especially in patients with Fanconi syndrome.

DISTAL RTA Pathophysiology

The cause of distal RTA involves failure of the distal tubule to synthesize new bicarbonate. Because bicarbonate production is functionally similar to H^+ secretion, many authors refer to distal RTA as the failure to excrete hydrogen or acidify the urine.^{4,30,31} In contrast to the self-limiting nature of proximal RTA, distal RTA is progressive and can lead to severe acidosis. Because

bicarbonate production is a stepwise process, failure of production can occur for a variety of reasons.

Voltage-dependent distal RTA occurs because of impaired sodium reabsorption^{4,37} (Figure 6). As previously discussed, sodium is normally reabsorbed into the distal tubule cell without the simultaneous transfer of an anion into the cell or a cation out of the cell. This type of transport creates a negatively charged tubular lumen that facilitates the transport of H⁺ and K⁺ out of the cell. Retaining both H⁺ and K⁺ inside the cell causes both metabolic acidosis and hyperkalemia.

The second step in bicarbonate production involves the action of the H⁺-ATPase pump. This condition, called *classic distal RTA*, can be either congenital or acquired. In contrast to voltage-dependent RTA, potassium levels in classic distal RTA are actually below normal. The independent movement of sodium into the distal tubule cell creates an electronegative charge in the tubule lumen. When H⁺ cannot be pumped out of the cell to neutralize this charge, the negative charge in the lumen remains relatively high. Because of the greater pull from the increased electronegativity of the distal tubule, more potassium is lost from the distal tubule cell into the tubular lumen.

The final cause of distal tubule RTA is related to increased permeability of the distal tubule membrane. In the normal distal tubule, the concentration gradient for hydrogen can be quite large as the hydrogen pump secretes ions into the lumen and the tubular membrane prevents the flow of these ions back into the cell down their concentration gradient. If this tubular membrane is compromised, H⁺ can pass back into the cell and combine with the hydroxide normally reserved for bicarbonate production. The leaky tubular membrane also facilitates the transfer of potassium into the tubular lumen and subsequently leads to potassium wasting. Hence, as with classic distal RTA, defects in membrane integrity result in metabolic acidosis with hypokalemia.

Clinical Signs

As with proximal RTA, distal RTA can result in signs associated with acidemia, including muscle weakness, inappetence, nausea, weight loss, stunted growth, and neurologic signs. In a 5-year-old mixed-breed dog diagnosed with distal RTA, the only clinical sign was anorexia.²⁹ If distal RTA is associated with hypokalemia, owners may report polyuria and polydipsia associated with hypokalemic nephropathy as well as muscle weakness.⁴ Increased urinary calcium excretion can also cre-

ate hyposthenuric urine and subsequent polyuria and polydipsia because urinary calcium can inhibit tubular sodium reabsorption, leading to sodium and water wasting. This sodium diuresis disrupts the normal counter-current mechanism that allows urine concentration. In addition, high urinary calcium can impair the water permeability in the collecting duct membrane, thus interfering with the action of antidiuretic hormone.⁹ When distal RTA is associated with another clinical disease (i.e., pyelonephritis, multiple myeloma, lupus), clinical signs attributable to the primary disease also occur.

Chronic metabolic acidosis can lead to osteomalacia by the same mechanism as described for bone buffering in proximal RTA. In humans, such bone changes are significantly more common in distal RTA than in proximal RTA; however, such pathology has not been reported in dogs and cats with distal RTA.

Along with bone destruction, distal RTA can also cause nephrolithiasis. As with proximal RTA, chronic metabolic acidosis associated with distal RTA causes leaching of calcium, phosphate, and bicarbonate from bone. However, unlike in proximal RTA, the urine in distal RTA is always alkaline and deficient in citrate. The reduced citrate decreases the solubility of calcium, while the high urine pH reduces the solubility of both calcium and phosphate. This reduced solubility combined with the increased urinary concentration of calcium and phosphate predisposes animals with distal RTA to stone formation. Although humans most frequently form calcium phosphate stones, both calcium oxalate and struvite uroliths can occur. A 1-year-old Labrador retriever evaluated at the University of Minnesota Veterinary Teaching Hospital was diagnosed with multiple struvite urocystoliths associated with distal RTA.²⁹

Diagnosis

An initial minimum database should provide sufficient information to warrant consideration of RTA. Hyperchloremic non-anion-gap metabolic acidosis with a urine pH greater than 5.5 to 6 suggests distal RTA; however, a urine culture should be conducted to ensure the changes are not due to the presence of urease-producing bacteria.^{10,29,31,38} The inability of the distal tubules to secrete H⁺ leads to metabolic acidosis. Hyperchloremia results from secretion of the conjugate base of the metabolic acid as a sodium salt, leading to volume contraction and subsequent retention of sodium and chloride. The clinician should ensure that the patient has neither diarrhea nor evidence of renal failure that could also cause normal

anion-gap acidosis. If these conditions are ruled out, further diagnostic testing is appropriate. Imaging modalities might reveal nephroliths, urocystoliths, and/or evidence of decreased bone density or, rarely, pathologic fractures. Urinalysis may reveal crystalluria, whereas a serum chemistry profile can show either hypokalemia or hyperkalemia.

A bicarbonate challenge test can be conducted in patients with normal urine pH when distal RTA is still suspected. Sodium bicarbonate should be given as previously described to diagnose proximal RTA, and urine CO₂ concentrations should be measured. Confirmation can be made when patients exhibit no increase in urine CO₂ levels despite the presence of large amounts of bicarbonate in the filtrate.

The diagnosis of distal RTA can also be confirmed with the ammonium chloride loading test. Because NH₄⁺ is an acid, when it is given orally, normal kidneys excrete excess H⁺ in the urine. In distal RTA, the kidneys fail to acidify the urine, leading to alkaline urine. Patients should be fasted for 8 hours and then given ammonium chloride at 0.1 g/kg PO. Two hours later, hourly urine sampling should begin and continue for 6 hours. Failure to collect urine on an hourly basis allows admixing of the urine and may lessen the decrease in urine pH.¹⁶ The pH of each collected sample should be measured immediately and recorded. A pH less than 5.5 rules out the presence of distal RTA. Failure of the urine pH to fall below 5.5 8 hours following administration of ammonium chloride confirms the diagnosis of distal RTA.¹⁶ In humans, the cut-off pH (range: 5.4 to 7) for determining the presence of RTA is controversial.¹⁰ This suggests that urine pH should not be looked at alone when confirming the diagnosis of distal RTA. Instead, it should be considered in light of the concurrent metabolic acidosis and the inability of the pH to drop despite excess total body hydrogen.

Causes

Although some of the causes of proximal and distal RTA are shared, there are some specific causes of distal RTA. For example, amphotericin B destroys the distal renal tubular membrane and is associated with the third type of distal RTA described. Pyelonephritis is a reported cause of distal RTA in both humans and small animals. Watson et al³⁷ reported distal RTA secondary to *Escherichia coli* pyelonephritis in a cat. A cat with chronic pyelonephritis was also found to have distal RTA in an earlier report by Drazner.³⁸ Systemic lupus erythematosus is also a reported cause of distal RTA in humans but has not been reported in veterinary patients.⁴ As with proximal RTA, distal RTA can also be associated with heavy metal toxicity, multiple myeloma, chronic hypocalcemic conditions, and outdated tetracycline administration.^{5,6}

Treatment

The bicarbonate dose required to correct metabolic acidosis associated with distal RTA is much less than that of proximal RTA. Empirical dosing of NaHCO₃ with careful monitoring is the usual method of therapy because of varying individual requirements. The recommended initial dose is 1 to 1.5 mEq/kg/day PO of sodium bicarbonate in divided doses.¹⁰ Acidosis is usually corrected with doses of 1 to 3 mEq/kg/day PO; however, higher doses may be required.³⁹ Sodium bicarbonate can be administered orally as

tablets, powder, or a solution. An 8-oz box of baking soda can be combined with 2.88 L of distilled water to create a 1 mEq/ml solution of bicarbonate.²⁷ Such a solution can be kept refrigerated for 2 months if capped.⁴⁰ As described for proximal RTA, if a patient is hypokalemic, potassium citrate might also be considered an alternative to bicarbonate therapy. If bicarbonate is used to correct acidemia, potassium gluconate elixir can be used as described for proximal RTA. The amount of potassium replacement should be adjusted according to individual need. In patients with nephroliths, serum potassium concentration should be closely monitored because of potential renal failure and concurrent hyperkalemia. Concurrent administration of vitamin D and calcium is not recommended because this may increase the tendency for urolithiasis. Alkali therapy usually allows fairly rapid correction of pH and serum bicarbonate; however, osteomalacia in humans may take several months to resolve. Appropriate antibiotic therapy should be administered for 4 to 6 weeks in patients with

reduce a dog's life span compared with that of unaffected dogs.³³ Furthermore, owners of these dogs believed their dogs had a good to excellent quality of life. Despite this, a fraction of dogs with Fanconi syndrome develop chronic renal failure, and, in this same study, this was the sole or predominant reason for euthanasia or death in 41% of affected dogs.³³ In addition, acute renal failure can occur and was described in a report of fatal uremia in a dog with Fanconi syndrome and resistant pyelonephritis.¹⁰

Even without complications such as urolithiasis or infection, and unless the condition is transient, management of RTA is lifelong and owners should be aware that frequent evaluation of their pet is necessary to assess its acid-base and electrolyte status.

CONCLUSION

RTA is an uncommon diagnosis in veterinary patients. The condition is characterized by non-anion-gap metabolic acidosis with a normal GFR. Proximal

Distal RTA occurs because of decreased bicarbonate production by the distal tubule.

pyelonephritis, with a follow-up urine culture to confirm resolution of the infection.

Patients should be seen every 1 to 2 weeks during initial alkali therapy to evaluate serum electrolytes, pH, and serum bicarbonate. The dose of bicarbonate or potassium citrate should be increased to return pH and serum bicarbonate to normal.¹² Once these values are stable, the patient should be reevaluated at least every 3 months to assess its metabolic status.

PROGNOSIS

The prognosis in patients with RTA is not well defined because of the few reports of this condition in the veterinary literature. The prognosis in patients with distal RTA is not as good as proximal RTA because patients with distal RTA are predisposed to urolithiasis. Although treatment and control of metabolic acidosis makes further urolithiasis and bone disease less likely, progressive renal damage from existing nephroliths or resistant infection can lead to renal failure. A recent review of 60 dogs with idiopathic Fanconi syndrome, 95% of which were basenjis, suggested that with the owners' meticulous care, the disease did not significantly

RTA is caused by decreased bicarbonate reabsorption in the proximal tubule and most commonly occurs in association with other proximal tubular defects. Distal RTA is associated with decreased production of bicarbonate by the distal tubule. Therapy for both conditions includes oral bicarbonate supplementation, although the requirement for patients with proximal RTA greatly exceeds that of those with distal RTA. Both proximal and distal RTA can be transient or permanent, depending on the underlying cause. Because of the acid-base and electrolyte derangements associated with the disease, routine biochemistry monitoring is recommended.

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ARTICLE #2 CE TEST



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1. RTA is characterized by

- a. anion-gap metabolic acidosis.
- b. azotemia and non-anion-gap metabolic acidosis.
- c. non-anion-gap metabolic acidosis and normal GFR.
- d. isosthenuria and azotemia.

2. Proximal RTA occurs because of

- a. failure of bicarbonate synthesis in the proximal tubule.
- b. decreased proximal tubular resorption of bicarbonate.
- c. increased acid production by the proximal tubule.
- d. increased acid load in the glomerular filtrate.

3. _____ is(are) not a reported cause of proximal RTA.

- a. Gentamicin
- b. Streptozotocin
- c. Heavy metals
- d. Cushing's disease

4. Fanconi syndrome

- a. is always a congenital condition.
- b. occurs only in basenjis.
- c. is associated with proximal RTA.
- d. is associated with distal RTA.

5. The diagnosis of proximal RTA can be based on

- a. the response to intramuscular injection of bicarbonate.
- b. a urine pH of 5.5 to 6 and hypochloremic metabolic acidosis.

- c. a urine pH greater than 6 following an intravenous constant-rate infusion of bicarbonate.
- d. metabolic acidosis in the absence of azotemia.

6. Bicarbonate therapy for proximal RTA

- a. requires very small amounts of bicarbonate.
- b. can lead to hyperkalemia.
- c. leads to further bicarbonate loss in the urine.
- d. does not require serum electrolyte monitoring.

7. Distal RTA is

- a. caused by decreased bicarbonate production by the distal tubule.
- b. always associated with acidic urine.
- c. self-limiting.
- d. caused by increased acid production by the distal tubule.

8. _____ is not a reported cause of distal RTA.

- a. Amphotericin B
- b. Enrofloxacin
- c. Outdated tetracycline
- d. Pyelonephritis

9. _____ may be used as an alternative to oral sodium bicarbonate in treating RTA.

- a. Potassium citrate
- b. Famotidine
- c. Calcium carbonate
- d. Omeprazole

10. In general, dogs with Fanconi syndrome are thought to have

- a. a poor quality of life.
- b. a shorter life span compared with that of unaffected dogs.
- c. only a very small chance of developing renal failure.
- d. a relatively good quality of life and normal life span.

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