39 Renal Tubular Acidosis

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Introduction

Renal tubular acidosis (RTA) is *a condition in which there is a defect in renal excretion of hydrogen ion, or reabsorption of bicarbonate, or both, which occurs in the absence of or out of proportion to an impairment in the glomerular filtration rate* (1). Thus, RTA is distinguished from the renal acidosis that develops as a result of advanced chronic kidney disease (2–4). Albright originally described the disease as "renal acidosis resulting from tubular insufficiency without glomerular insufficiency" to emphasize this distinction (5). The term was reduced to "renal tubular acidosis" by Pines and Mudge in their studies published in 1951 (6). These renal tubular abnormalities can occur as an inherited disease or can result from other disorders or toxins that affect the renal tubules.

Historical Development of Classification of RTA

The historical development of renal tubular acidosis parallels the historical development of our understanding of renal physiology. As with many complex diseases, investigations into disease processes improve our understanding of normal physiology and, in turn, the advances in basic physiologic research shed light on pathophysiology and mechanisms of diseases. This is apparent in the historical development of renal tubular acidosis which began in the early twentieth century and is now extending into the molecular biologic era as medicine enters the twenty-first century. In addition, some of the confusion with the classification scheme of RTA stems from its historical development.

At the British Pediatric Association meeting in 1935, Lightwood described six infants out of an autopsy series of 850 that had "calcium infarction" of the kidneys (7). This would later be recognized as the first report of infants with nephrocalcinosis from renal tubular acidosis. Butler et al. described a series of four infants with similar findings in 1936 (8). In addition to nephrocalcinosis, these infants were also found to have hyperchloremia and acidosis, suggesting that there was a relationship between the biochemical findings and nephrocalcinosis. It was not clear from these first reports if the biochemical findings were the cause of the calcium deposits in the kidneys or were the result of damage to the renal tubules from the calcinosis.

The first description of the potential pathophysiologic explanation for these findings was put forward by Albright, et al. in 1946 (5). In this classic description of various forms of osteomalacia, the authors also outlined the treatment of these patients with a solution of citric acid and sodium citrate that was advocated by Dr Shohl. Albright described this form of acidosis as "renal acidosis resulting from tubular insufficiency without glomerular insufficiency" to distinguish this form of acidosis from the acidosis that occurs in renal failure.

The entity of "infantile renal acidosis" was then described by Lightwood in 1953 in a series of 35 infants (9). This was a larger series of infants than his first description and they had similar clinical histories and biochemical findings as the series by Butler (8). The first description of an adult with similar findings was made in 1945 by Baines, et al. (10).

During the 1940s and 1950s, a number of cases of renal tubular acidosis were described and led to investigations of the renal acidification defect (4, 11). The primary feature in these patients was the inability to lower their urine pH despite having mild to moderate acidosis. This became the defining characteristic of this disease as reported in a series of studies by Elkinton (12, 13). In the classic report by Pines and Mudge, the term "renal tubular acidosis" was used to replace the previously more cumbersome term of "renal acidosis resulting from tubular insufficiency without glomerular insufficiency" (6). This new term was emphasized in an editorial review by Elkinton and has remained the term for this disease ever since (12). Thus, at the end of the 1950s, renal tubular acidosis was thought to be a disease process that limited the ability of the kidneys to lower the urine pH, despite the fact that the patient had mild to moderate acidosis.

Although the concept of glomerular filtration had been well established in the early twentieth century, the measurement of the rate of glomerular filtration in humans had not been performed. This was accomplished

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by the pioneering work of Homer Smith. He was one of the first to conceive of the idea of a renal excretion system in which there was a high glomerular filtration rate which required tubular reabsorption of solutes (14). The fact that the glomerular filtration rate was very high and was followed by tubular modifications of the urine had profound effects on the ideas of bicarbonate handling and acid secretion.

The disorder of renal tubular acidosis was initially thought to be due to the inability of the kidney to maintain the steep pH gradient in the distal nephron segment. The idea that this disorder could arise from the inability of the proximal tubule to recover the filtered bicarbonate was first suggested in 1949 by Stapleton (15). He reported a patient that had significant amounts of bicarbonate in the urine at low concentrations of serum bicarbonate. This idea was further advanced by Soriano in a report of two patients that demonstrated an abnormally low threshold for bicarbonate excretion (16, 17). Based on their findings in these patients, Soriano and Edelmann proposed classifying patients with RTA as having either distal or proximal tubule defects. This was the initial description of the need for a classification scheme for this disease, suggesting that there could be multiple causes for this disease process.

The dichotomy of proximal and distal RTA was firmly established in the classic review by Rodriguez-Soriano and Edelmann which summarized the understanding of the pathophysiology at that time (1). The nomenclature of type I and type II RTA was established by the end of the 1960s in a review by Morris (18). In this review, distal RTA was referred to as type I (or classic) and proximal RTA as type II. The author also described a type III RTA as those patients that displayed features consistent with both forms of RTA. In 1972, McSherry, et al. described several patients that displayed characteristics of classic type I RTA but in addition had a reduced threshold for bicarbonate reabsorption. These patients seemed to fit the description of type III RTA. Subsequently, the reabsorption of bicarbonate in these patients normalized so that they were thought to have classic type I RTA with a developmental immaturity of the proximal tubule. Since that time, type III RTA has been essentially dropped from the classification scheme of RTA. It is interesting to note that the review by Genarri and Cohen did not mention type III RTA (19).

In the middle of the twentieth century, the discovery of aldosterone revolutionized our understanding of the physiology of sodium and potassium metabolism (20). Subsequently, it was found that patients with aldosterone deficiency had a form of RTA that resembled that of distal RTA, but the patients had hyperkalemia and not hypokalemia (21, 22). This form of RTA was then referred to as type IV RTA. More recently, other defects in distal nephron transporters have also been characterized and resemble the findings of type IV RTA. Although they are not true aldosterone deficient syndromes, they also are described as type IV RTA since these patients also have hyperkalemia. To add to the confusion, a review published in 1986 classified RTAs as type I (distal), type II (proximal) and type III (aldosterone deficient RTA) (23).

In recent years, there have been suggestions to clarify the classification of RTAs in a scheme that is based more on the pathophysiologic mechanism of the disease (24, 25). While this might eventually be the preferred nomenclature, most practicing nephrologists continue to use the historical classification. The other schemes will be discussed as part of the pathophysiology of RTA.

Over the past century, advances in renal physiology, acid-base chemistry, and molecular genetics have greatly improved our understanding of the various forms of renal tubular acidosis. Currently, the diagnosis and classification of the various types of renal tubular acidosis continue to rely on biochemical measurements of blood and urine. During the twenty-first century, however, the diagnosis of renal tubular acidosis may eventually be made by a molecular genetic approach and not by extensive biochemical testing.

Physiology of Acid Secretion

The kidney is the primary organ for long term acid base regulation. Thus, an understanding of the normal renal excretion of acid is necessary to understand the defects present in patients with RTA.

The typical Western diet generates approximately 1 mmol of H^+ per kilogram of body weight in adults (26). In addition, children generate acid from the production of hydroxyapatite in growing bone and thus generate a total of approximately 2–3 mmol of H^+ per kilogram of body weight (27–29). The acid generated from the diet and bone growth necessitates the excretion of acid by the kidneys.

The amount of acid excreted by the kidneys is referred to as Net Acid Excretion (NAE) and is expressed quantitatively as:

$$NAE = \left(U_{NH_4^+} + U_{TA} - U_{HCO_3}\right) \times V,$$

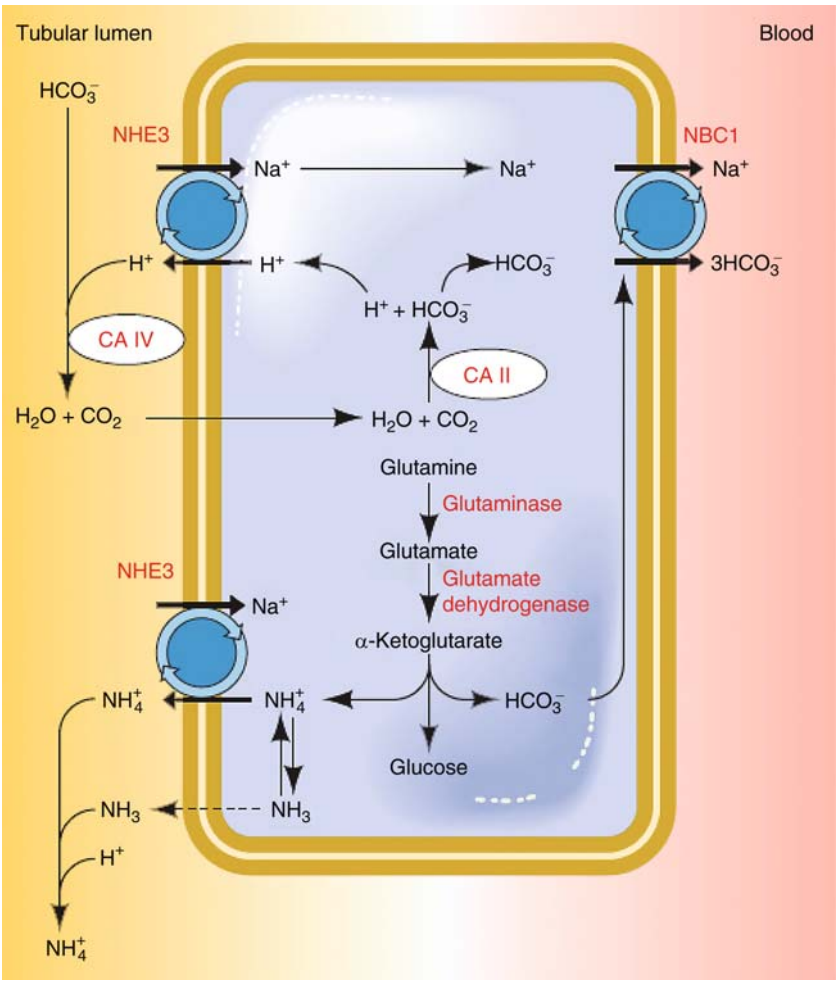
where V is the urine flow rate, $U_{NH_4^+}$ is the urine ammonium concentration, U_{TA} is the urine titratable acid concentration and U_{HCO_3} is the urine bicarbonate

concentration. Thus, the components of acid secretion can be thought of as bicarbonate reclamation to prevent bicarbonate loss, ammonium excretion and titratable acid excretion. The processes for maintaining acid base balance are quite complex, but the basic concepts will be reviewed so that the pathophysiologic changes in RTA can be described.

The kidneys are responsible for the excretion of nitrogenous waste products, principally urea, that are generated from our diet. In mammalian kidneys, urea is excreted primarily by filtration which requires having a high filtration rate so this can be accomplished. The average adult will filter about 150–180 L of blood per day. Because bicarbonate is freely filtered in the glomerulus, a large amount of bicarbonate (about 4,000 mEq per day in an adult) must be reabsorbed by the tubules each day to prevent loss of base. The bulk of the filtered bicarbonate is reabsorbed in the proximal tubule by mechanisms that are illustrated in *Fig. 39-1*. A number of proteins, both transporters and enzymes, work in

Figure 39-1

Model of bicarbonate reabsorption by a proximal tubule cell. The Na-K-ATPase located in the basolateral membrane generates and maintains the low intracellular sodium concentration. Protons are excreted into the tubule lumen by the sodium-proton exchanger (NHE3) where they combine with bicarbonate to form carbonic acid. In the presence of carbonic anhydrase IV (CAIV) the carbonic acid is hydrolyzed to water and carbon dioxide which enter the cell and recombine to form carbonic acid by the action of intracellular carbonic acid II (CAII). The carbonic acid ionizes into a proton which is then excreted into the lumen and bicarbonate which is transported by the sodium-bicarbonate symporter (NBC1) into the blood stream (reprinted with permission from (30)).



concert to reclaim approximately 80% of the filtered bicarbonate in this tubule segment (31–33).

The initial step in the reabsorption of bicarbonate is the secretion of protons into the tubular lumen. About two thirds of the proton secretory rate is provided by the sodium-proton antiporter (34–36). The isoform that is present on the luminal membrane of the proximal tubule has been termed NHE3 (sodium hydrogen exchanger 3). The energy for proton secretion by the antiporter is derived from the low intracellular sodium concentration that is maintained by the basolaterally located sodium-potassium ATPase. There is evidence that approximately one third of the proton secretory rate is provided by a proton ATPase located in the luminal membrane (36, 37). This transporter derives its energy directly from ATP.

Once the hydrogen ion is in the lumen of the proximal tubule, it combines with bicarbonate to form carbonic acid which will then form carbon dioxide and water as shown in the following equation:

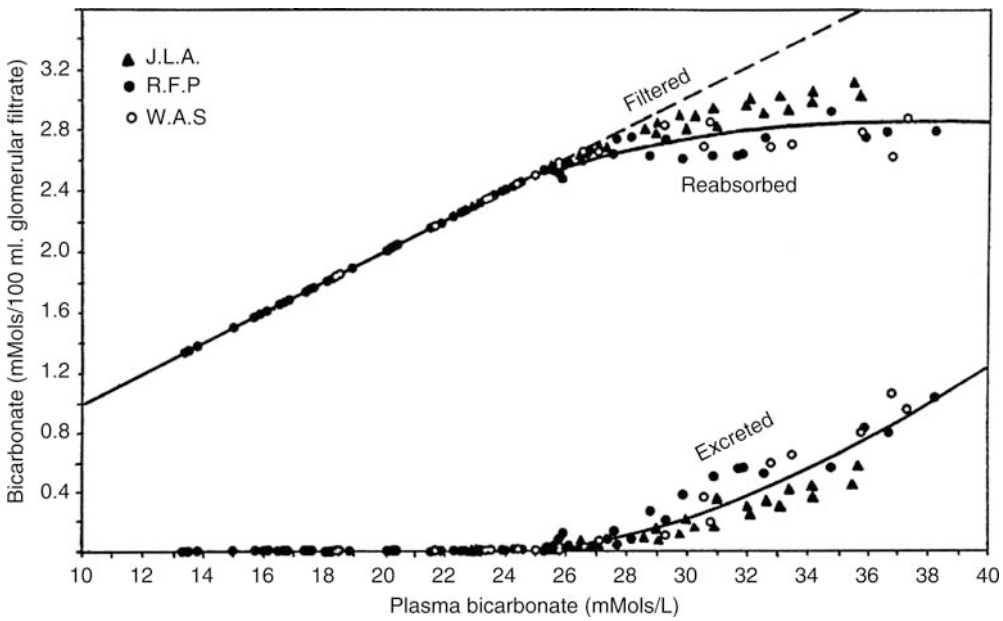
$$H^+ + HCO_3^- \longleftrightarrow H_2CO_3 \xleftrightarrow{\text{carbonic anhydrase}} H_2O + CO_2$$

The enzyme, carbonic anhydrase, is critical for catalyzing this process (38–40). One isoform of this enzyme (carbonic anhydrase IV) is located in the brush border membrane of the proximal tubule and serves to catalyze the forward reaction while another isoform of the enzyme (carbonic anhydrase II) is located inside the tubule cell for catalyzing the reverse reaction (38). Thus, carbon dioxide and water can move rapidly into the proximal tubule cell and recombine to form carbonic acid which will ionize to form bicarbonate and a hydrogen ion. The hydrogen ion is then available for secretion into the tubule lumen while the bicarbonate ion is then transported through the basolateral membrane by the sodium-bicarbonate cotransporter, NBC (41–43).

The overall process for reabsorbing bicarbonate in the proximal tubule is saturable (44). This is illustrated in *Fig. 39-2*. When the serum bicarbonate concentration is within the normal range, the filtered load of bicarbonate can be almost completely reabsorbed. If the serum bicarbonate concentration begins to rise, the filtered load of bicarbonate will then exceed the reabsorption rate of the kidney and bicarbonate will then be excreted into the urine. This has been studied in humans who were administered bicarbonate to determine the point at which bicarbonate would appear in the urine (44). The data from these experiments form a titration curve (see *Fig. 39-2*). The normal serum concentration of bicarbonate is thus determined by the threshold at which bicarbonate is excreted.

Figure 39-2

Bicarbonate titration curves for normal humans. At low concentrations of serum bicarbonate, all of the filtered load can be reabsorbed. The process of bicarbonate reabsorption is saturable, so once the delivered bicarbonate rate exceeds the transport maximum, bicarbonate will be excreted in the urine (reprinted with permission from (45)).



An additional task in maintaining acid base balance for the proximal tubule is the generation of ammonia to serve as a buffer to efficiently excrete the bulk of the acid that is generated from our diet. It has long been recognized that the excretion of ammonium is critical to the overall excretion of acid by the kidneys (46). This is primarily due to ammonium's ability to buffer hydrogen ions. To excrete 100 mmol of unbuffered H^+ at a pH of 4.0 ($[H^+] = 10^{-4}$ mol/L) would require a volume of 1,000 L of urine. The reaction of ammonia and H^+ to form ammonium has a pKa of approximately 9.0 (47). Thus, at a pH of 7.0, 99% of all the ammonia in the urine is in the form of ammonium ion and is excreted as ammonium chloride, limiting the amount of free hydrogen ions in the urine. Thus, the ammonium excretion rate is a quantitatively more important factor for the excretion of acid than the urine pH.

This can also create confusion in the assessment of a patient's ability to excrete acid. The equation that defines net acid excretion (see above) does not include information about the urine pH. Since the pKa of the ammonia/ammonium equilibrium is nine, if the patient is excreting a large amount of protons as ammonium, the pH will tend to rise even though the amount of acid being excreted has increased.

The tubular handling of ammonia and ammonium is complex (48–50). Briefly, ammonia is generated in the proximal tubule by the metabolism of glutamine and is secreted into the tubule lumen by the sodium-proton exchanger as the ammonium ion (see *Fig. 39-1*). The diffusion of ammonia gas across the proximal tubule apical membrane accounts for a small fraction of the total excretion of ammonia. The ammonium ions are then reabsorbed into the interstitium by the thick ascending limb of Henle to be secreted again by the collecting ducts (50, 51). The generation of ammonia by the proximal tubule can be upregulated in the presence of acidosis by 5- to 10-fold over baseline in adults (46, 52, 53). The ability of the neonatal kidney to upregulate ammonium excretion is somewhat limited and can prolong the recovery phase of acidosis in infants. The upregulation of ammonium production and secretion serves as the principal means of correcting acidosis that is due to non-renal causes. As will be seen below, the inability of the kidney to secrete acid as ammonium is a key feature of RTA.

The thick ascending limb of Henle is responsible for continued reabsorption of bicarbonate as well as ammonium (54, 55). The transporters involved include the sodium-hydrogen exchanger (NHE3), the sodium-potassium-2 chloride cotransporter, NKCC2 and the sodium-potassium ATPase (54). The thick ascending limb of Henle reabsorbs approximately 10% of the filtered bicarbonate.

The distal nephron is responsible for the secretion of protons which are then buffered by ammonia and titratable acid. The cell type in the collecting duct that is responsible for this is the alpha intercalated cell that is depicted in *Fig. 39-3*. The luminal membrane has a proton ATPase that utilizes ATP directly to secrete protons into the lumen of the tubule (56–59). This generates a bicarbonate ion that is then excreted through the basolateral membrane by the anion exchanger AE1 in exchange for a chloride ion (60, 61). The chloride can then exit the cell by the potassium chloride cotransporter (KCC) or the chloride channel, CLC-Kb (62, 63). Carbonic anhydrase II is critical for the formation of the carbonic acid in the cell that ionizes into the proton and bicarbonate ion (39).

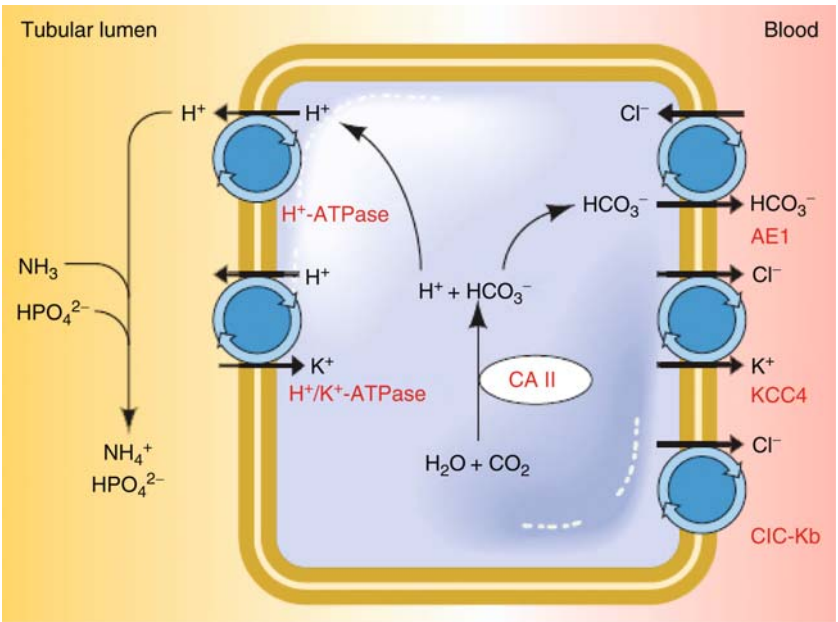
The principal cells of the collecting duct are responsible for the reabsorption of sodium and the secretion of potassium and thus do not directly secrete protons into the tubular fluid. However, these processes influence the rate of acid secretion indirectly by affecting the electrical potential difference across the epithelium. Thus, disease processes or drugs that have a primary effect on sodium or potassium transport in the collecting duct can eventually lead to acid base disturbances.

As discussed above, the proximal tubule generates ammonia that is eventually excreted as ammonium as a mechanism for acid excretion. The other major buffers in the urine are referred to as titratable acids and include phosphate, sulfate and many other anions. Of the many buffers available, the quantitatively most significant is phosphate. Phosphate exists in the blood as several different ionic species (H_3PO_4, $H_2PO_4^{-1}$, HPO_4^{-2} and PO_4^{-3}) with $H_2PO_4^{-1}$ and HPO_4^{-2} being the most abundant at physiologic pHs. The pK for the equilibrium between $H_2PO_4^{-1}$ and HPO_4^{-2} is 6.8, thus at a normal blood pH of 7.4, the ratio of $H_2PO_4^{-1}$: HPO_4^{-2} is approximately 4:1. As the urine passes through the collecting duct where the pH is lower, HPO_4^{-2} can accept protons and be converted to $H_2PO_4^{-1}$ and will aid in the buffering of excreted acid.

In addition to bicarbonate reabsorption and ammonia generation, the proximal tubule reabsorbs almost the entire filtered load of glucose and amino acids as well as approximately 85% of the filtered load of phosphate. These processes are coupled to the apical membrane sodium electrochemical gradient and are thus driven by the low intracellular sodium concentration and the negative electric potential inside the cell. Diseases that affect

Figure 39-3

Model of acid excretion in an alpha-intercalated cell in the distal nephrons. Protons are excreted into the tubule lumen by the proton-ATPase and are buffered by ammonia or titratable acid (mostly phosphate). Inside the cell, carbonic anhydrase II (CAII) provides the protons and bicarbonate through the hydration of carbon dioxide to form carbonic acid. Bicarbonate is excreted into the blood stream by action of the chloride bicarbonate exchanger (AE1) on the basolateral membrane. Chloride homeostasis is maintained by the potassium-chloride cotransporter (KCC4) and the chloride channel (ClC-Kb) (reprinted with permission from (30)).



the ability of the proximal tubule cell to maintain this gradient result in a condition known as the Fanconi syndrome (64). This is a form of proximal tubule dysfunction that includes proximal RTA, glucosuria, amino aciduria and phosphaturia. As will be discussed below, most forms of proximal RTA are associated with the Fanconi syndrome.

Proximal Renal Tubular Acidosis (Type II RTA)

Pathophysiology

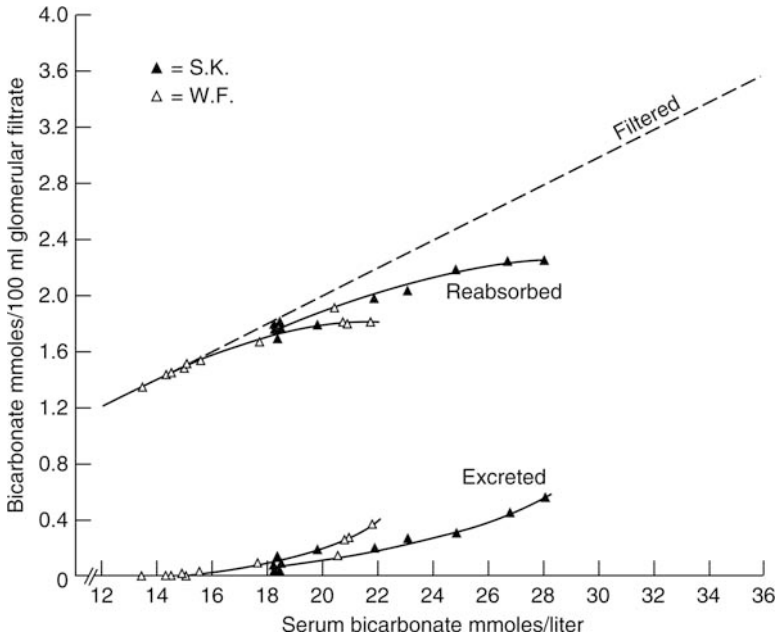
As discussed above, the transport of bicarbonate in the proximal tubule is a saturable process. Thus, the transport of bicarbonate exhibits the typical titration curve which has a threshold for bicarbonate reabsorption as illustrated in *Fig. 39-2* (44). This threshold for the reabsorption of bicarbonate is the main factor determining the serum bicarbonate concentration. If the serum bicarbonate concentration rises above the threshold, the filtered load will exceed the transport maximum for reabsorption and bicarbonate will be excreted. This will bring the serum concentration down until it matches the threshold and then all of the filtered bicarbonate is again reabsorbed.

The hallmark of proximal RTA is a reduced threshold for the reabsorption of bicarbonate as illustrated in *Fig. 39-4* and thus, these patients will have a low serum bicarbonate concentration (17, 66). When the serum bicarbonate concentration increases and approaches the normal range, patients with proximal RTA will develop bicarbonaturia. Their bicarbonate titration curve is similar to that of normal patients, but it is shifted to the left (see *Fig. 39-4*). It is important to note that the threshold for bicarbonate excretion is generally in the 14–18 mEq/L range and remains stable (1, 17).

This reduction in the capacity for reabsorption of bicarbonate makes the treatment of patients with proximal RTA difficult. Most patients require well over 6 mEq/kg/day of bicarbonate therapy to make an improvement in their serum bicarbonate concentration (67, 68).

Figure 39-4

Bicarbonate titration curves for patients with proximal renal tubular acidosis. Patients with proximal RTA have a reduced threshold for bicarbonate reabsorption and will thus excrete significant amounts of bicarbonate in their urine at lower serum bicarbonate concentrations. Thus, their titration curves are shifted to the left (reprinted with permission from (65)).



As the patient is treated with bicarbonate and the serum bicarbonate rises, bicarbonate excretion will increase dramatically with little increase in the serum bicarbonate concentration. In addition, the distal delivery of the non-reabsorbable anion will obligate the excretion of sodium and potassium. This leads to volume depletion and an increase in the serum aldosterone concentration (69). The combination of the increased distal delivery of sodium and the elevated aldosterone concentration leads to a marked excretion of potassium. Thus, many patients with proximal RTA become hypokalemic during the treatment of the disease.

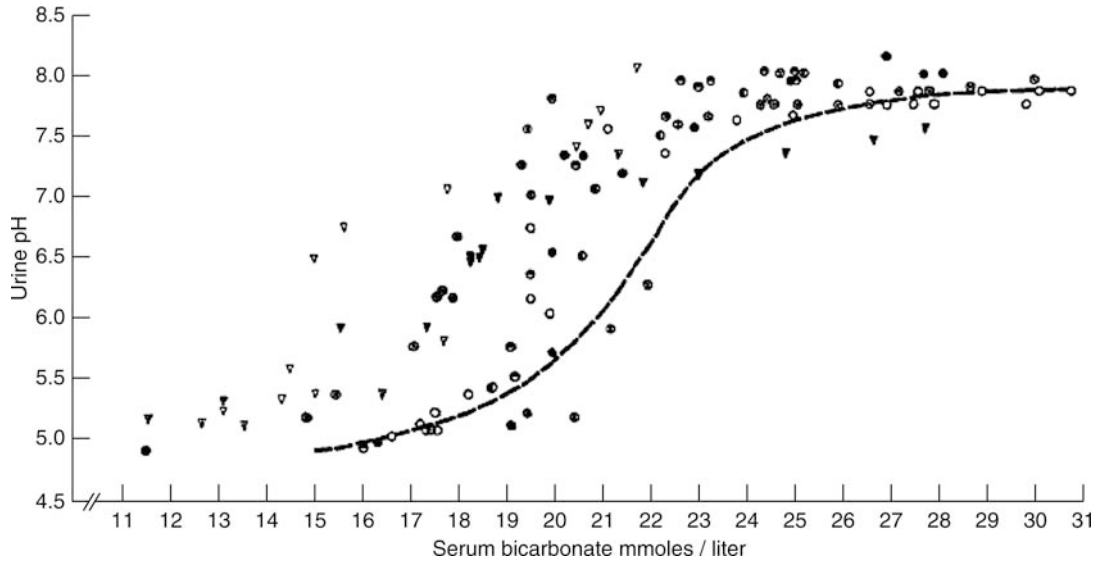
Although the treatment of these patients can be difficult, their overall acid base balance is generally good. In patients with proximal RTA, when the serum bicarbonate remains at or below the threshold for bicarbonate excretion, the patient can reclaim the filtered load of bicarbonate and will remain in relative acid base balance (16, 17, 67). This is due to the fact that the patient's distal nephron remains intact and is able to excrete the acid generated from their diet and will help prevent the patient from developing a large base deficit. This is reflected in the fact that their urine pH can decrease to less than five (*Fig. 39-5*) (1). Thus, while most patients with proximal RTA have a low serum bicarbonate, it will remain constant because the patient remains in acid base balance.

The acid base balance of patients with pure proximal RTA has been extensively studied (67, 68). At baseline, the patients were found to be in acid base balance with normal ammonium and titratable acid excretion and did not develop a base deficit. When challenged with an ammonium chloride load, they were able to increase the excretion of acid in the form of ammonia as well as titratable acid (67).

While the excretion of ammonium increased in this study, it is unclear if patients with proximal RTA have the same capacity to increase ammonia excretion as normal individuals. Because the proximal tubule is the site of ammoniagenesis, there could conceivably be a defect in the ammonia generation rate. When these patients were loaded with ammonium chloride, their excretion of acid was increased; however, the ratio of ammonia excretion to titratable acid excretion remained constant (16, 17, 67). This brought into question their ability to increase ammonia excretion in the face of an acid load and thus would probably not be able to recover from acidosis as well as a normal patient would. It was also thought that the

Figure 39-5

Urine pH of patients with proximal RTA. When patients with proximal RTA become acidotic, their serum bicarbonate concentration falls below the threshold for excretion. Because their distal nephron is intact, they can lower their urinary pH to values less than 6.0 (reprinted with permission from (70)).



level of ammonium excretion could be considered low for the chronic acidotic state (67).

A more recent study has indicated that while patients with proximal RTA are in balance at baseline, when their acidosis worsens, they cannot fully compensate (71). In this study, patients with proximal RTA were loaded with ammonium chloride for 3 days. Previous studies had been performed with an acute ammonium chloride load. The chronic loading demonstrated that the patients with proximal RTA indeed had an inability to increase their ammonium excretion as compared to the normal control subjects (71). Interestingly, the patients with proximal RTA were able to lower their urine pH to a value below the control subjects' urine pH (4.66 vs. 5.00). This was thought to be due to the fact that the normal subjects had higher amounts of ammonium in their urine to buffer the protons.

The mechanism for the ability to maintain acid base balance is due in part to an increase in titratable acid excretion (67). Because of their intact distal nephrons, these patients can also lower their urine pH to the 4.5–5 range. However, this usually occurs at very low serum pH values and is depicted in *Fig. 39-5* (1).

Calcium excretion rates in patients with proximal RTA were found to be within the normal range, indicating that there was no loss of calcium from their bones (67, 68). There was also no evidence of rickets or osteomalacia in these patients with isolated proximal RTA (67).

Fanconi Syndrome (See also Chapter 42)

As discussed above, the proximal tubule is also responsible for the reabsorption of glucose, amino acids and phosphate by sodium dependent transport systems. Many of the processes that interfere with the reclamation of bicarbonate are due to a defect in maintaining a low intracellular concentration of sodium and will thus affect the reabsorption of all of these solutes. This condition is known as the Fanconi syndrome which can be thought of as a global dysfunction of the proximal tubule (64). Thus, proximal RTA can be divided into isolated proximal RTA, which is relatively rare, and Fanconi syndrome, which is actually a more common cause of proximal RTA. This will be an important point in the clinical presentation and work up of these patients.

In addition to the problems with bicarbonate wasting, patients with Fanconi syndrome have additional pathophysiologic changes. The original definition of Fanconi syndrome consisted of skeletal findings secondary to hypophosphatemia (i.e., rickets), generalized

aminoaciduria and glucosuria (64). Later, it was found that the tubular reabsorption of bicarbonate was impaired and the definition then included proximal RTA (1). Recent reports indicate that severe osteomalacia can develop in adult patients with Fanconi syndrome (72, 73). Hypokalemia also develops in most patients with this disorder (30).

There are numerous diseases that present with Fanconi syndrome, but they appear to have a final common pathway for the proximal tubule dysfunction. A number of studies have indicated that depletion of the intracellular ATP store is responsible for the loss of the transmembrane sodium gradient (74, 75). This then leads to the inability to secrete protons and reabsorb glucose, phosphate and amino acids.

Etiology

As with most clinical disease processes, isolated proximal RTA and Fanconi syndrome can occur as an inherited defect or as an acquired disease. We will first discuss the congenital causes of this syndrome, and then review the acquired causes.

Congenital Isolated Proximal RTA

As mentioned above, isolated proximal RTA is rare (76). The initial descriptions of isolated proximal RTA were of infants that had a transient form of the disease (1, 68, 77). This form was found predominately in males and appeared to improve after several years of life. Patients presented with failure to grow and repeated bouts of vomiting and dehydration. This form follows a sporadic inheritance pattern and has no known cause.

There is a well described kindred of patients from Puerto Rico that have isolated proximal RTA that follows an autosomal dominant pattern of inheritance (67). To date, there are no reports of a gene defect in this family. Interestingly, the patients are more severely affected as infants, but tend to have less of a problem when they are older. This suggests that either the defect is attributable to a developmental transporter or to compensation with age by other transport processes in the more distal nephron segments. Children in these families have moderate acidosis and do not grow at normal rates unless they receive treatment (67). As discussed above, treatment with alkali therapy does not fully correct their acidosis because of the increased excretion of the administered base, but treatment will allow them to grow at near normal rates.

In recent years, another family with isolated proximal RTA that has an autosomal dominant inheritance pattern has been reported (78). The clinical features of this family were very similar to the previous report (67). A candidate gene approach was taken in an attempt to determine the genetic defect in this family. Extensive sequencing was done on many of the genes known to be involved in the proximal tubule reabsorption of bicarbonate; carbonic anhydrase II and IV as well as carbonic anhydrase XIV; NBC1; NHE2, NHE3 and NHE8 as well as the sodium proton exchanger regulatory proteins NHRF1 and NHRF2; and the chloride bicarbonate exchanger, SLC26A6. However, no defects were found. The authors concluded that either additional proteins are involved in the regulation of bicarbonate reabsorption or that there might have been defects in transcription factors that could regulate the expression of these genes (78).

A rare cause of isolated proximal RTA is a mutation in the sodium bicarbonate cotransporter, NBC1, which is inherited in an autosomal recessive pattern (79–81). The initial patients described were two brothers that had proximal RTA as well as eye and dental abnormalities (82). Since then, only a few other patients have been described with these features (82, 83). These patients were found to have a defect in the sodium bicarbonate cotransporter, NBC1, that is responsible for transporting bicarbonate out of the proximal tubule cell and into the blood stream (80, 83–85). Although these cases are very rare causes of isolated proximal RTA, they have demonstrated the critical function of NBC1 in the proximal tubule reabsorption of bicarbonate.

The sodium bicarbonate cotransporter, NBC1, is in the class of transporters that are critical in the membrane transport of bicarbonate known as SCLA4 (60, 61, 86–88). This class also includes the chloride bicarbonate exchanger that will be discussed in the section on distal RTA. The sodium coupled bicarbonate transporter in the proximal tubule cotransporter is designated SCLA4A4 (NBC1) and is also found in other tissues such as the eyes as well as the heart (80). This kidney specific isoform is determined by alternate splicing of the gene. Defects in this transporter result in proximal RTA due to the inhibition of bicarbonate transport in the proximal tubule. Because of the distribution of the protein in the eye, patients also develop ocular defects (80). Recently it was found that the defect might be in trafficking of the protein and not the actual function of the protein (89).

Defects in carbonic anhydrase cause dysfunction of the proximal tubule, but because of its distribution in the distal nephron, these defects cause combined proximal

and distal RTA (43, 90). These will be discussed in detail below in the section on Type III RTA.

The sodium hydrogen exchangers have been considered candidate genes for the cause of isolated proximal RTA, however, to date there have been no defects found in these genes. To determine the role of these exchangers in overall acid base balance, knockout mouse models have been generated. The primary sodium hydrogen exchanger in the apical membrane of the proximal tubule is NHE3 (34). Mice that have had NHE3 knocked out have a modest metabolic acidosis (91). They have an elevated serum aldosterone level as well as upregulation of colonic sodium transporters indicating that these animals have evidence of volume contraction (91). Perfusion of the proximal tubules in vitro shows a reduced ability to acidify the urine (92). As discussed above, a recent study in patients with isolated proximal RTA failed to detect a defect in any known gene for bicarbonate transport including NHE3 (78).

Another mouse model of proximal RTA was developed recently (93). The TASK K + channel is located in the proximal tubule and appears to regulate bicarbonate transport. When this channel was knocked out, the animals developed acidosis which was due to renal bicarbonate wasting (93).

Congenital Fanconi Syndrome

There are a number of genetic defects that result in Fanconi syndrome. These are listed in *Table 39-1* and will be described briefly.

The most common cause of congenital Fanconi syndrome is cystinosis which is an autosomal recessive disorder (94, 95). This disease results from a defect in the gene CTNS which encodes for the lysosomal membrane transporter, cystinosin (96, 97). Lysosomes are organelles responsible for degradation of proteins within the cell. Cystinosin is responsible for the transport of cystine out of the lysosome so that the organelle can continue to function. In the disease cystinosis, cystine accumulates within the lysosome of the cells throughout the body (95). It is not clear how this leads to the Fanconi syndrome, but it appears to be related to depletion of intracellular ATP (74, 75).

The other diseases that result in the Fanconi syndrome are much rarer. One in particular is worth mentioning because it is thought to be the cause of the syndrome first described by Fanconi (98–102). This is a defect in the facilitative glucose transporter GLUT2. This transporter is responsible for transporting glucose out of the proximal tubule cell and into the blood stream. Thus, a mutation in this protein would lead to accumulation of glucose within the proximal tubule. It is unclear how this would cause the Fanconi syndrome, but could be due to the consumption of intracellular phosphate by the accumulated glucose.

Table 39-1
Inherited causes of Fanconi syndrome

Disease	Gene defect	OMIM
Cystinosis	Cystinosin (CTNS)	219,800
Tyrosinemia	Fumarylacetoacetase	276,700
Fanconi-Bickel syndrome	Glut 2	138,160
Hereditary fructose intolerance	Fructose-1-phosphate aldolase	229,600
Dent's disease	ClCN5	300,009
Lowes syndrome	Phosphatidylinositol 4,5-bisphosphate 5-phosphatase deficiency (OCRL1)	309,000
Galactosemia	Galactose-1-phosphate uridylyltransferase	230,400
Wilson's disease	ATPase, Cu^{2+}-transporting, beta polypeptide	277,900

Hereditary fructose intolerance is of interest because this served as a useful model for the study of Fanconi syndrome (103, 104). The cause of the Fanconi syndrome in this disorder is thought to be due to the depletion of intracellular phosphate that occurs when the cell is presented with a load of fructose. Patients with this disorder tend to have normal renal function and no acid-base disturbance when they remain on a fructose restricted diet.

The oculo-cerebro-renal syndrome of Lowe is due to a mutation in the OCRL1 gene which encodes for the enzyme, phosphatidylinositol 4,5-bisphosphate 5-phosphatase (105). This causes an accumulation of phosphatidylinositol 4,5-bisphosphate in the cells which presumably leads to the Fanconi syndrome because it interferes with actin polymerization (106). The syndrome is inherited in an X-linked pattern.

Dent disease is caused by mutations in the chloride channel encoded by the gene, CLCN5 (107–110). The original term for this disorder was X-linked hypercalciuric nephrolithiasis. The chloride channel that the gene encodes for is found in intracellular organelles and appears to be critical for maintaining pH gradients. It is not clear how this defect results in the Fanconi syndrome.

Other diseases that lead to the Fanconi syndrome include galactosemia and tyrosinemia (111–114). These disease processes can also be controlled by diet. Rarely, other forms of glycogen storage disease can result in the Fanconi syndrome (115–117). Mitochondrial defects can also rarely be associated with the Fanconi syndrome (118–121).

Recently, mutations in the transcription factor HNF1 alpha have been associated with dysfunction of the proximal tubule (122). In addition, these defects result in maturity onset diabetes of the young type 3 (MODY3) (123). This syndrome has been reproduced in a mouse model (124). Thus, it appears that this transcription factor is a key regulator of glucose metabolism and could impact the function of the proximal tubule.

Acquired Isolated Proximal RTA

Most diseases and toxins that affect the proximal tubule result in the Fanconi syndrome, thus it is rare for isolated proximal RTA to be acquired. The primary cause of isolated proximal RTA is inhibition of carbonic anhydrase (CA) (125). Acetazolamide is given to treat pseudotumor cerebri and some forms of glaucoma. One side effect of this treatment is the development of proximal RTA. Indeed, this is often used as a marker of treatment adequacy. A number of other medicines can also cause CA inhibition, e.g., hydrochlorothiazide and topiramate (126–129).

Acquired Fanconi Syndrome

There are many toxins and medications including heavy metals that are now known to affect the proximal tubule and result in the Fanconi syndrome (130–133). In particular, a number of well documented cases of Fanconi have been reported with valproic acid (134, 135). These appear to be reversible processes, but the time of resolution can be significant. Chinese herbs containing aristolochic acid have also been associated with Fanconi syndrome (136, 137). Other agents that have been associated with Fanconi syndrome include aminoglycosides, ifosfamide, the antiviral agent tenofovir and salicylate (138–145).

Disease processes that cause the Fanconi syndrome are either immune mediated diseases or paraproteinemia syndromes. For example, Sjogren's disease will typically cause distal RTA but has been reported to cause Fanconi syndrome (146). The classic paraproteinemia that results in Fanconi syndrome is multiple myeloma (147–149).

Other conditions that are associated with Fanconi syndrome include vitamin D deficiency (150, 151). The mechanism of action for this process is not well understood. In addition, proximal RTA has been reported in pregnancy and with paroxysmal nocturnal hemaglobinuria (152, 153).

Distal Renal Tubular Acidosis (Type 1 RTA)

Pathophysiology

The hallmark of distal RTA is the inability to lower the urine pH maximally in the face of moderate to severe systemic acidosis (1). This is clearly shown in *Fig. 39-5* where the urine pH is graphed against the serum bicarbonate concentration. As can be seen in the normal individuals, the urine pH decreases to a value of approximately 4.5–5.0, but the patients with distal RTA fail to reduce their urine pH below 6.5. While this feature has been known for many years and was the initial defining characteristic of RTA, the causes of this dysfunction have only recently been elucidated (*Fig. 39-6*).

The primary function of the distal nephron in acid base homeostasis is excretion of the acid generated by the metabolism of our diet. As described earlier, the typical western diet generates approximately 1 mmol of acid per kilogram of body weight (26). Children have an additional 1–2 mmol of acid per kilogram body weight that is generated from the formation of hydroxyapatite in growing bone. Thus, the distal nephron in the growing child has the task of excreting between 1 and 3 mmol of acid per kilogram (27–29). If the distal nephron is not capable of performing this function, the patient will use the existing buffers in the body to buffer this acid. Most of the pathophysiologic consequences of distal RTA are due to accumulation of acid. Even though the proximal tubule is functioning normally to reabsorb the filtered load of bicarbonate, the patient will continue to accumulate acid and develop an ever increasing base deficit.

After the bicarbonate buffers in the extracellular fluid space are depleted, the bones begin to serve as the buffer source for the accumulated acid. Hydroxyapatite can be dissolved to liberate hydroxyl ions to help in the neutralization of the acid. Studies in patients with distal RTA have shown that they are in negative calcium balance due to the reabsorption of bone (1). This will lead to nehrocalcinosis and nephrolithiasis.

Another contributing factor to the development of nephrocalcinosis is the fact that citrate reabsorption in the

Figure 39-6

Urine pH of patients with distal RTA. Because patients with distal RTA cannot excrete hydrogen ions against a gradient in the distal nephron, they are unable to significantly lower their urine pH, even when they become very acidotic (reprinted with permission from (70)).

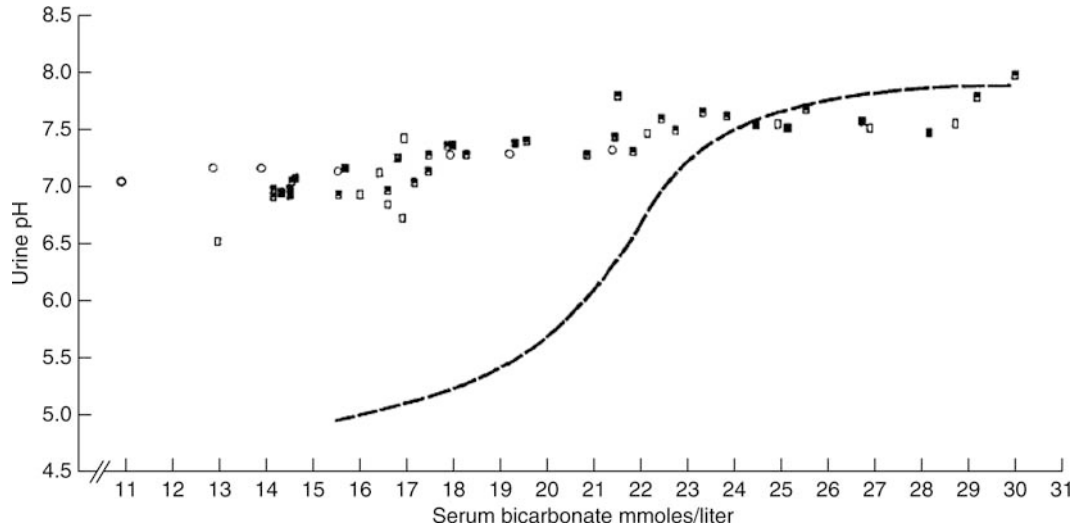
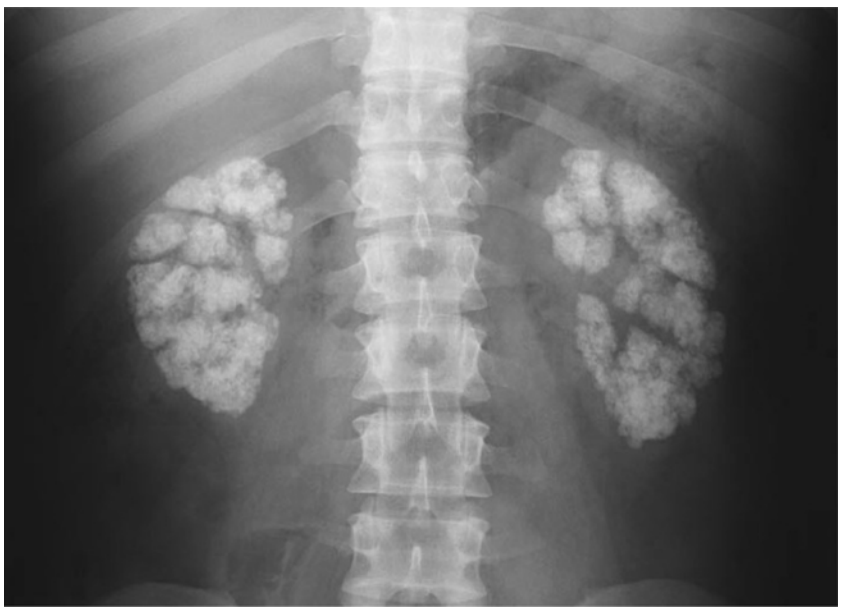


Figure 39-7

Nephrocalcinosis in a patient with distal RTA (reprinted with permission from (156)).



proximal tubule will be increased to help provide for base equivalents (154, 155). The resulting hypocitraturia will contribute to the development of nehrocalcinosis and nephrolithiasis. This can be used to help differentiate distal RTA from proximal RTA as seen in *Fig. 39-7* (157). In growing bones, the acid base disturbance will lead to rickets whereas in the older patient, they will develop osteomalacia. The description of this was provided by Albright (5).

Nephrocalcinosis has also been associated with increased production of red cells (158, 159). It is not clear what the mechanism is in these patients. Erythrocytosis has been observed in some patients with distal RTA, presumably as a result of the nephrocalcinosis (158, 159).

The proximal tubule provides ammonia that is delivered to the distal nephrons to serve as a buffer. Recently, it has been appreciated that the rate of ammonium excretion in patients with distal RTA is less than that of normal subjects (24, 25, 160). This is presumably due to the fact that ammonia that is not converted to ammonium ion by the secretion of protons can then diffuse back into the blood stream and is subsequently not excreted. There have been a number of reports of patients with distal RTA that have hyperammonemia at the time of presentation when they are extremely acidotic (161–163). They do not have liver dysfunction but they have an inability to excrete the ammonia generated in the proximal tubule.

This phenomenon has lead some investigators to postulate that the excretion of ammonium be used as a new classification scheme of RTA (160). While this could result in a more physiologic scheme for the classification of RTA, this is probably not practical at the present time. The measurement of ammonium in the urine is not a routine laboratory test. Methods for estimating ammonium excretion will be discussed in the section on clinical aspects.

Another pathophysiologic finding in patients with classical distal RTA is hypokalemia (164, 165). The exact mechanism for this is not entirely clear but is at least partially due to elevated aldosterone concentrations in these patients (45). Careful studies have indicated that the aldosterone concentration is routinely elevated in patients with distal RTA. A few patients had aldosterone concentrations in the normal range, but were inappropriately normal for the degree of hypokalemia. It was thought that the patients were mildly volume depleted because of mild proximal tubule dysfunction. The hypokalemia can be severe and cause muscle paralysis (166). This has occasionally been the presenting sign of RTA (167).

Etiology

Congenital

Congenital forms of distal RTA are divided into autosomal dominant (type Ia) and autosomal recessive with (type Ib) and without (type Ic) hearing loss. The molecular basis for these forms of inherited distal RTA have become clear over the past few years and have greatly improved our understanding of the molecular basis of renal acid base metabolism.

Autosomal dominant distal RTA is caused by mutations in the anion exchanger (AE1) that is located in the basolateral membrane of the alpha intercalated cells of the collecting duct. This exchanger is responsible for the basolateral exit of bicarbonate into the blood stream. Thus, if the protein is not functioning, acid secretion into the tubule lumen will be limited.

The biology of AE1 has proven to be very interesting (60, 168, 169). The exchanger is also located in the red cell membrane where it was first discovered and was termed "band 3 protein" (169). While it serves to function in the red blood cell as an anion exchanger, it also binds to other membrane proteins and contributes to the stability of the red cell membrane. Thus, defects in AE1 have been associated with hereditary spherocytosis and south-east Asian ovalocytosis (SAO) (168). In general, patients with these disorders do not have RTA.

The mutations in AE1 that result in autosomal dominant distal RTA are located in a different area of the molecule than the mutations causing the red cell membrane defects (170, 171). Patients with autosomal dominant distal RTA tend to develop a less severe form of RTA than patients with the autosomal recessive forms (172, 173). Most of the patients do not have red cell membrane defects. However, there have been recently described patients with both RTA and SAO. These patients were found to be compound heterozygotes for mutations that cause the two different disorders or they were homozygous for a mutation that could cause both RTA and SAO (174–176).

The autosomal recessive distal RTA with hearing loss (type Ib) was found to be due to mutations in a subunit (ATP6V1B1) of the proton pump located on the apical membrane of the alpha intercalated cell of the collecting duct (177). This led to the discovery of the proton pump location in the inner ear (178, 179). The proton pump is a key transporter in the secretion of hydrogen ions (56–59). It is a complex molecule with multiple subunits that are specific to the location in the body.

Subsequent to the initial discovery, a number of other mutations have been discovered that are responsible for autosomal recessive distal RTA with hearing loss (70, 180). Most recently, a large family with this form of RTA and hearing loss had been reported (181). The defect has been recently determined to be a truncating mutation of the ATP6V1B1 which prevented the subunit from organizing with the rest of the proton pump for complete function (182).

As families were characterized for mutations in the proton pump, it was clear that some of the families did not have hearing loss and did not have defects in the ATP6V1B1 subunit. This led to the designation of autosomal recessive distal RTA without hearing loss (type Ic). Defects in a separate subunit (ATP6N1B) were found to be the cause in the initial families studied (183). Subsequently, a number of patients developed hearing loss later in life. These patients were found to have a defect in subunits that were found in the inner ear (180).

Mouse models of distal RTA have also been developed. A mouse model that lacks AE1 (slc4a1) has been produced and found to have many of the same features as the human disease (184). The importance of the potassium chloride transporter KCC4 for function of the alpha intercalated cells was shown in a knock out model (62). These mice had features of distal RTA. A mouse that lacked the transcription factor Foxi1 was shown to have distal RTA (185). This transcription factor is evidently important in the development of the alpha intercalated cells. There are no known human mutations in this factor, but the mouse model raises the possibility of this being another gene to consider in human disease.

Acquired

The most common cause of acquired distal RTA is immunologic destruction of the alpha intercalated cells. This occurs most frequently with Sjogren's syndrome (186, 187). Distal RTA in Sjogren's has been reported to occur in about one third of the patients and after a duration of 10 years (187, 188). It can also occur in patients with systemic lupus erythematosis and has been reported in a patient with Graves' disease (189–192). Distal RTA has also been reported in renal transplant patients, however it is not clear if this is immune mediated or secondary to the medications (193).

A number of medications have been found to cause distal RTA. The classic example is amphotericin (194). This model has been used to study the pathogenesis of RTA in the laboratory (195, 196). The primary defect in acid secretion due to amphotericin appears to be an increase in the permeability of the collecting duct cells to hydrogen ions. This would then prevent the formation of the gradient that is necessary to secrete protons into the urine. While these results helped explain the pathophysiology of the backleak and is important clinically, this probably does not apply to patients with inherited defects that result in distal RTA.

Other medications that are known to cause distal RTA include lithium, foscarnet and melphalan (197–199). The mechanisms for these effects are not clear.

Acquired distal RTA can also result from the treatment of hypophosphatemic rickets (200). This is probably a result of the nephrocalcinosis that develops form the high dose of vitamin D these patients receive. Examination of patients with idiopathic hypercalciuria also demonstrated some defects in renal acidification (201).

An interesting association of distal RTA and ingestion of vanadate has been proposed as a mechanism for the high endemic rate of RTA in northeastern Thailand (202). These patients develop severe hypokalemia and it is thought that this could be due to inhibition of the H-K-ATPase by vanadate. There is a high level of vanadate in the soil in this area and experiments with rats have shown that administration of vanadate can lead to renal tubular acidosis (203).

Glue sniffing has been listed as a cause of distal RTA; however careful examination of a patient with acidosis form glue sniffing suggests a different cause of the acidosis (204). The toluene in the glue is rapidly metabolized to hippuric acid which is promptly excreted by the kidneys. When measurements were made of ammonium excretion rates, they were found to be normal. Thus, the conclusion is that while there might be some renal tubule damage from the glue sniffing, the bulk of the acidosis results from hippuric acid production. The prompt excretion of the hippurate prevents the development of an increase in the anion gap (204).

Type III Renal Tubular Acidosis

Type III RTA refers to a form of renal tubular acidosis that has features of both proximal RTA and distal RTA. During the middle of the twentieth century, a number of patients were found to have features of both forms of RTA and the third type of RTA was suggested. It was subsequently found that these patients had distal RTA with a transient form of proximal RTA. Thus, the term fell out of favor and had not been used.

More recently, a form of RTA that occurs with some forms of osteopetrosis has been characterized that seems to meet the criteria for the designation of Type III RTA. This association was originally described in 1972 (205). Subsequently, the defect was found to be a mutation in the gene for carbonic anhydrase II (43, 90). After the initial finding of the genetic defect, a number of other patients have been described with similar clinical findings

(156, 206, 207). These patients have other extrarenal findings such as cerebral calcifications as well as the bone problems associated with osteopetrosis (207). It should be pointed out that osteopetrosis can be caused by a defect in a number of different genes that affect the osteoclast (208). Thus, the finding of osteopetrosis does not imply that the patient will have a defect in carbonic anhydrase II and will develop RTA. The form of osteopetrosis associated with the carbonic anhydrase deficiency is the syndrome known as Guibaud-Vainsel syndrome or marble brain disease (208).

Type IV Renal Tubular Acidosis

The effects of aldosterone on electrolyte balance have been extensively studied since the discovery of aldosterone in the 1950s (20). The initial findings demonstrated dramatic effects of aldosterone on sodium reabsorption and potassium secretion. In the latter half of the twentieth century it became clear that aldosterone also had effects on acid base balance. With the recent advances in molecular biology, the mechanisms involved in the genetic causes of type IV RTA have been elucidated.

Type IV RTA was initially used to describe patients that developed acidosis from aldosterone deficiency. This could occur as an inherited defect, such as congenital adrenal hyperplasia, or could be acquired as in Addison's disease. The principal feature that distinguished type IV RTA from classic type I RTA was the finding of hyperkalemia. Patients with type IV RTA are hyperkalemic while many of the patients presenting with classic type I RTA were hypokalemic. This led investigators to believe that the cause of this form of RTA was aldosterone deficiency. Later it became apparent that many of the patients were not aldosterone deficient, but had a decreased responsiveness of the renal tubules to aldosterone and hence developed hyperkalemic RTA. Currently the term type IV RTA is applied to all forms of hyperkalemic RTA, regardless of the serum aldosterone concentration.

Pathophysiology

The primary effect of aldosterone on the collecting duct is to stimulate sodium reabsorption and potassium secretion in the principle cells (209). This results in an enhancement of the lumen negative electrical potential which can then help promote proton secretion. Aldosterone also has direct effects on the alpha intercalated cells to promote proton secretion by upregulating expression of the proton ATPase as well as carbonic anhydrase (209). The effect of aldosterone on ammonia excretion is not clear. There is evidence that aldosterone deficiency could directly inhibit the production of ammonia while other studies indicate that the effect could be secondary to hyperkalemia (210–212). Ammonia secretion in patients with aldosterone deficiency was low and was shown to increase after administration of mineralocorticoid; however, it was still not clear if the effect could be secondary to changes in potassium concentration.

Patients that are aldosterone deficient or resistant to the actions of aldosterone have increased excretion of sodium which leads to volume depletion and potentially a decrease in the glomerular filtration rate (213, 214). Thus, many of the symptoms of this process are secondary to the volume depletion.

The acidosis in most patients with type IV RTA is not as severe as in other forms of RTA (213). Thus, the main clinical problem with most of these patients is the hyperkalemia. Treatment often relies on restricting the intake of potassium but will ultimately depend on the cause of the RTA.

Etiology

As discussed above, type IV RTA can result from a deficiency of aldosterone or from a resistance of the renal tubules to the actions of aldosterone.

Aldosterone Deficiency

Aldosterone deficiency can be the result of a global dysfunction of the adrenal gland, referred to as Addison's syndrome, or it can be the result of isolated aldosterone or mineralocorticoid deficiency. The most common inherited form of mineralocorticoid deficiency is congenital adrenal hyperplasia (CAH) which is due to 21-hydroxylase deficiency (65, 215). Other infants can present with isolated aldosterone synthase deficiency which is not as severe a disease process since the glucocorticoid pathway remains intact (216).

Aldosterone Resistance

There are a number of inherited and acquired conditions that result in resistance of the tubules to the action of aldosterone. The pathway for aldosterone action includes the mineralocorticoid receptor and the epithelial sodium

channel (ENaC). Defects in both of these components results in type IV RTA. Because of the renal tubular resistance to aldosterone, aldosterone concentrations in the blood are quite elevated. Thus, this is referred to as pseudohypoaldosteronism (PHA).

Defects in the mineralocorticoid receptor lead to an autosomal dominant form of PHA (217). This form is the least severe of the PHAs and patients tend to improve as they get older. This is presumably due to compensation by other pathways to reabsorb sodium and secrete potassium and hydrogen ions.

An autosomal recessive form of PHA is due to defects in ENaC (218). Patients with this form can be severely affected since the final pathway for sodium regulation in the collecting duct involves ENaC. In addition, they have severe pulmonary problems at birth because ENaC is present in the lungs and is a key factor in the reabsorption of fluid from the lung space after birth.

Both of these forms of PHA lead to salt loss and volume depletion. Patients tend to be hypotensive and dehydrated. Additionally, plasma concentrations of renin and aldosterone are quite elevated because of the volume depletion.

A form of PHA that occurs in patients that are hypertensive was originally thought to be due to a "chloride shunt" in the collecting duct and was referred to as PHA type 2 or Gordon's syndrome (219). These patients are characterized by having hyperkalemia and acidosis, but have a low concentration of renin and aldosterone in their plasma. This led investigators to hypothesize that the paracellular pathway in the collecting duct was allowing chloride to be reabsorbed at a higher rate than was needed (220). This would cause the electrical potential difference in the tubule to decrease and would thus decrease the excretion of potassium and protons.

Recent discoveries have shown that PHA type 2 is due to defects in WNKs (with no lysine kinases) (221). Specifically, there are families with the syndrome that have mutations in WNK1 and some with mutations in WNK4. The biology of the WNKs has turned out to be very complicated and is beyond the scope of this chapter. However, they seem to be key players in the regulation of potassium and blood pressure.

Acquired

Addison's disease can be an autoimmune disease or can be the result of damage to the adrenal gland from infection or infarction. Treatment involves replacing the adrenal hormones as needed as well as treating the underlying infection. In adult patients, diabetes is a leading cause of type IV RTA as a result of hyporeninemic hypoaldosteronism (222). There are other disease processes that also lead to a decrease in production of renin which would then lead to a decrease in aldosterone secretion. If the patient has type IV RTA from acquired hypoaldosteronism, treatment with mineralocorticoids will correct the defect (223).

Tubular resistance to aldosterone can occur as a result of a number of different processes. Autoimmune diseases can lead to interstitial nephritis that decreases the tubule responsiveness to aldosterone (224). Patients with systemic lupus erythematosis classically develop type 1 RTA, but have been reported to present with type IV RTA (192). Infections such as acute pyelonephritis can also cause a resistance to aldosterone action.

Probably the most common cause of acquired type IV RTA in the pediatric age range is obstruction of the urinary tract. The mechanism by which obstruction causes resistance of the tubule to aldosterone is not clear, but this is commonly seen in patients with posterior urethral valve or with prune belly syndrome.

Type IV RTA can also been seen in patients with a renal transplant (225). This could be due to either an immune mediated mechanism or it could be related to medications used for the treatment of rejection. In particular, calcineurin inhibitors are known to cause a type IV RTA (193, 226).

Other medications that are known to interfere with the action of aldosterone include angiotensin converting enzyme inhibitors (ACE inhibitors), heparin, prostaglandin inhibitors (NSAIDs) and a number of potassium sparing diuretics. These would include amiloride which blocks the epithelial sodium channel and spirinolactone which blocks the mineralocorticoid receptor.

Clinical Aspects of Renal Tubular Acidosis

The diagnosis of renal tubular acidosis represents a challenge to the clinician for a number of reasons. Depending on the severity of the disease presentation, the patient could present with findings consistent with proximal and distal RTA. The patients are also many times quite volume depleted at presentation and it is not clear how much this impacts the serum chemistries. In addition, patients with infections can be septic and in shock. Thus, the complete evaluation of a patient for renal tubular acidosis might have to occur after the acute illness has subsided.

As with any complex disease, the diagnosis of RTA begins with clinical suspicion. If the disease is not being considered in the differential diagnosis, then a definitive diagnosis will not be made. There have been a number of recent reviews that outline practical guidelines for the diagnosis and management of RTA (227–230). This section of the chapter will focus on the reasoning behind the laboratory testing that is recommended for the work up of patients with suspected RTA.

The inherited forms of renal tubular acidosis present almost uniformly with failure to grow and repeated episodes of vomiting and dehydration (1, 68). It should be emphasized that most of these patients are very ill appearing at the time of presentation. The patient with failure to grow that otherwise appears healthy ahs a much lower probability of having RTA. A recent study examined patients referred for failure to thrive that had serum chemistries indicating the possibility of RTA (231). Simply performing a venous blood gas analysis in the patients demonstrated the absence of acidosis.

The first step in the evaluation of patients with an acidosis is to determine the serum anion gap (232–234). Patients with RTA are characterized by having a normal anion gap. This is also referred to as a hyperchloremic metabolic acidosis. Interpretation of the anion gap can occasionally be misleading. Other factors can affect the anion gap such as serum protein concentrations, calcium and other anions such as phosphate (233). Thus, the determination of a normal anion gap acidosis can only be correctly made when these factors are taken into account.

Although renal tubular acidosis should be suspected in these patients with metabolic acidosis with a normal anion gap, there are other disorders to consider in the differential diagnosis such as gastrointestinal loss of bicarbonate. The workup of these patients is therefore designed to differentiate whether the acidosis is of renal or extrarenal origin. Thus, it is necessary to examine the response of the kidney to the metabolic acidosis. As discussed above, the normal renal response to metabolic acidosis is to increase ammonium chloride excretion as a way to enhance hydrogen ion excretion to correct the acidosis. Unfortunately, measuring ammonium in the urine is not a routine function in most hospital laboratories. Over time, several approaches have been taken to estimate the urinary excretion of ammonium to determine if the kidney is responding normally (235–239).

The measurement of the urine pH can be helpful but also can be misleading in the diagnosis of RTA (240). Where it tends to be helpful is in determining whether or not there is bicarbonate in the urine (see *Fig. 39-8*).

The simplest test that was devised is to measure the urine sodium, potassium and chloride concentrations and calculate the urinary anion gap using the following equation:

$$Urinary\ anion\ gap = U_{Na} + U_K - U_{Cl},$$

where U_{Na} is the urinary sodium concentration, U_K the urinary potassium concentration and U_{Cl} the urinary chloride concentration. This approach is based on the fact that the unmeasured cations and anions are constant and that ammonium would be the primary cation other than sodium and potassium that would be excreted with chloride. The amount of ammonium in the urine when the anion gap is zero turned out to be 80 mmol/L. The other assumptions in this approach are that there is no appreciable bicarbonate in the urine and the patient is not receiving medications that are excreted in the urine in ionic form such as penicillins. If the urine pH is less than seven, the urinary bicarbonate will be less than 10 mmol/L (see *Fig. 39-8*). This simple approach has been verified in normal controls as well as patients with RTA and gastrointestinal causes of acidosis (235, 237).

Modifications to the urinary anion gap calculation have been made to expand its application to conditions that could yield misleading results. If patients are excreting other anions, ammonium would be excreted with the unmeasured anion instead of chloride. Thus, the urinary anion gap would underestimate the amount of ammonium in the urine. The osmolal gap was developed to take this into account (238). The osmolal gap is calculated by the following equation:

$$Urine\ osmolal\ gap = measured\ urine\ osmolality - calculated\ osmolality.$$

The calculated osmolality is determined by the following equation:

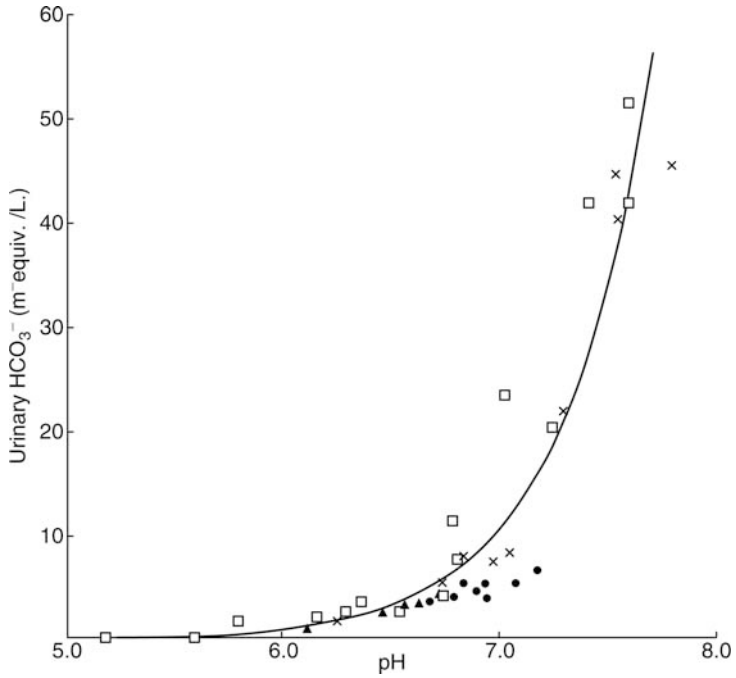
$$\text{Calculated osmolality} = \text{Na} + \text{K} + \text{HCO}_3 + \text{urea nitrogen}/2.4 + \text{glucose}/18.$$

This was shown to correctly account for the unmeasured anions in patients with ketoacidosis (238). An additional modification was then developed because of the difficulty in measuring the urine bicarbonate concentration. This method replaces the urine bicarbonate measurement by multiplying the sum of the sodium and potassium concentrations by two (236).

The above approaches are designed to estimate the amount of ammonium in the urine. Normal controls have about 80 mmol/L of ammonium in the urine (237). What makes the test work well in the evaluation of acidosis is

Figure 39-8

Urinary bicarbonate concentration as a function of urinary pH. As can be seen, once the urine pH becomes less than 6.5, the concentration of bicarbonate is less than 10 mEq/L. This might have an impact in determining the urinary anion gap (reprinted with permission from (241)).



the fact that normal individuals will have an increase in their ammonium excretion but the patients with RTA will not. A recent study examined the correlation of these techniques with actual measurement of urinary ammonium (242). This study concluded that the correlation many times was not good and that direct measurement of the urinary ammonium would be a better method. Another problem with this approach is that neonates were found to have a poor correlation between urinary anion gap and urinary ammonium concentration (243).

Another approach to examine the urine for proton secretory rate is to measure the urine and blood pCO_2 during bicarbonate loading (244–246). The idea is to take advantage of the low level of carbonic anhydrase activity in the distal nephron. When the patient is loaded with bicarbonate, the delivery to the proximal tubule will exceed the transport maximum and significant amounts of bicarbonate will be delivered to the distal nephron. If the patient has a normal proton secretory rate, hydrogen ions will be secreted into the tubule lumen. Although there is CA II in the distal nephron, the rate of reaction is slow enough that the carbon dioxide will be excreted in the urine and not reabsorbed. Under these conditions, normal individuals will have a urinary pCO_2 of greater than 70 mm Hg or a blood-urine pCO_2 of greater than 30 mm Hg. Patients with a defect in hydrogen ion secretion will have a urinary pCO_2 of less than 70 mm Hg or a blood-urine pCO_2 of less than 30 mm Hg. This method has been shown to be useful in neonates as well as adults (246).

Other tests might be indicated if the results of the above remain indeterminate. Traditionally, the patient's ability to acidify the urine is tested using acute or chronic loading with ammonium chloride (228). Because of the unpalatable nature of the ammonium loading, urinary acidification can be evaluated using a combination of a mineralocorticoid and furosemide (247).

Differentiating Proximal and Distal RTA

Once it has been determined that the patient has RTA, it is necessary to determine if it is a proximal or distal defect. Usually this can be determined by the associated findings in the patient. As outlined above, most patients with proximal RTA have the Fanconi syndrome. Thus, it is

very helpful to evaluate the urine for glucosuria and phosphaturia. If these are normal but the patient is suspected of having a proximal tubule defect, it might be necessary to perform a bicarbonate titration to find the threshold for bicarbonate excretion (228). The serum potassium concentration will also help determine if the patient has a type IV RTA.

Another useful determination is a renal sonogram or X-ray to determine if the patient has nephrocalcinosis (see *Fig. 39-7*). Patients with distal RTA have hypocitraturia and therefore are much more likely to have nephrocalcinosis and form renal stones. Patients with proximal RTA are in relative acid base balance so that they have normal amounts of citrate in their urine and they do not excrete large amounts of calcium.

Treatment

The treatment of RTA will of course be determined by the type and cause of RTA. Fanconi syndrome due to cystinosis should be treated with cysteamine (241, 248, 249). This will prevent further damage to the renal tubular cells by preventing the accumulation of cystine. However, these patients continue to have Fanconi syndrome and require large amounts of alkali therapy as well as phosphate and vitamin D.

The sporadic forms of proximal RTA are also difficult to correct completely, but mild improvements in their acid base status allows them to grow normally (67). These patients tend to improve with age and will need less alkali as the grow.

The treatment of distal RTA is somewhat more straight forward. The amount of alkali needed to correct the acidosis and maintain normal acid base balance is much less than that needed in patients with proximal RTA. The dosage of alkali necessary has been recently studied. Using potassium citrate, investigators have found that 3–4 mEq/kg/day was necessary to normalize the urinary citrate excretion (250, 251). A previous study had also indicated that the dosage of alkali needed to be higher in younger children and decreased to about 3 mEq/kg/day after the age of 6 years (69).

The importance of continued therapy in these children has been a recent concern (252). It appears that subclinical acidosis could have long term effects on the bone, resulting in osteoporosis. The loss of calcium from the bones would also lead to nephrocalcinosis and renal stone formation.

References

1. Rodriguez-Soriano J, Edelmann CM, Jr. Renal tubular acidosis. *Annu Rev Med* 1969;20:363–382.
2. Davies HE, Wrong O. Acidity of urine and excretion of ammonium in renal disease. *Lancet* 1957;273:625.
3. Schwartz WB, Hall PW, III, Hays RM, Relman AS. On the mechanism of acidosis in chronic renal disease. *J Clin Invest* 1959;38:39–52.
4. Wrong O, Davies HE. The excretion of acid in renal disease. *Q J Med* 1959;28:259–313.
5. Albright F, Burnett CH, Parson W, Reifenstein EC, Jr, Roos A. Osteomalacia and late rickets. *Medicine* 1946;25:399–479.
6. Pines KL, Mudge GH. Renal tubular acidosis with osteomalacia; Report of 3 cases. *Am J Med* 1951;11:302–311.
7. Lightwood R. Calcium infarction of the kidneys in infants. *Arch Dis Child* 1935;10:205.
8. Butler AM, Wilson JL, Farber S. Dehydration and acidosis with calcification at renal tubules. *J Pediatr* 1936;8:489–499.
9. Lightwood R, Payne WW, Black JA. Infantile renal acidosis. *Pediatrics* 1953;12:628–644.
10. Baines AM, Barelay JA, Cooke WT. Nephrocalcinosis associated with hyperchloremia and low plasma-bicarbonate. *Q J Med* 1945;14:113–123.
11. Reynolds TB. Observations on the pathogenesis of renal tubular acidosis. *Am J Med* 1958;25:503–515.
12. Elkinton JR. Renal acidosis. *Am J Med* 1960;28:165–168.
13. Elkinton JR, Huth EJ, Webster GD, Jr, McCance RA. The renal excretion of hydrogen ion in renal tubular acidosis I quantitative assessment of the response to ammonium chloride as an acid load. *Am J Med* 1960;29:554–575.
14. Berliner RW. Homer Smith: his contribution to physiology. *J Am Soc Nephrol* 1995;5:1988–1992.
15. Stapleton T. Idiopathic renal acidosis in an infant with excessive loss of bicarbonate in the urine. *Lancet* 1949;1:683–685.
16. Rodriguez SJ, Boichis H, Stark H, Edelmann CM, Jr. Proximal renal tubular acidosis. A defect in bicarbonate reabsorption with normal urinary acidification. *Pediatr Res* 1967;1:81–98.
17. Soriano JR, Boichis H, Edelmann CM, Jr. Bicarbonate reabsorption and hydrogen ion excretion in children with renal tubular acidosis. *J Pediatr* 1967;71:802–813.
18. Morris RC, Jr. Renal tubular acidosis. Mechanisms, classification and implications. *N Engl J Med* 1969;281:1405–1413.
19. Gennari FJ, Cohen JJ. Renal tubular acidosis. *Annu Rev Med* 1978;29:521–541.
20. Williams JS, Williams GH. 50th anniversary of aldosterone. *J Clin Endocrinol Metab* 2003;88:2364–2372.
21. Perez GO, Oster JR, Vaamonde CA. Renal acidosis and renal potassium handling in selective hypoaldosteronism. *Am J Med* 1974;57:809–816.
22. Perez GO, Oster JR, Vaamonde CA. Renal acidification in patients with mineralocorticoid deficiency. *Nephron* 1976;17:461–473.
23. Rocher LL, Tannen RL. The clinical spectrum of renal tubular acidosis. *Annu Rev Med* 1986;37:319–331.
24. Carlisle EJ, Donnelly SM, Halperin ML. Renal tubular acidosis (RTA): recognize the ammonium defect and pH or get the urine pH. *Pediatr Nephrol* 1991;5:242–248.
25. Halperin ML, Goldstein MB, Richardson RM, Stinebaugh BJ. Distal renal tubular acidosis syndromes: a pathophysiological approach. *Am J Nephrol* 1985;5:1–8.

26. Halperin ML, Jungas RL. Metabolic production and renal disposal of hydrogen ions. *Kidney Int* 1983;24:709–713.
27. Chan JC. The influence of dietary intake on endogenous acid production. Theoretical and experimental background. *Nutr Metab* 1974;16:1–9.
28. Chan JC. Calcium and hydrogen ion metabolism in children with classic (type I/distal) renal tubular acidosis. *Ann Nutr Metab* 1981;25:65–78.
29. Kildeberg P, Engel K, Winters RW. Balance of net acid in growing infants. Endogenous and transintestinal aspects. *Acta Paediatr Scand* 1969;58:321–329.
30. Sebastian A, McSherry E, Morris RC, Jr. On the mechanism of renal potassium wasting in renal tubular acidosis associated with the Fanconi syndrome (type 2 RTA). *J Clin Invest* 1971;50:231–243.
31. Alpern RJ. Cell mechanisms of proximal tubule acidification. *Physiol Rev* 1990;70:79–114.
32. Boron WF. Acid-base transport by the renal proximal tubule. *J Am Soc Nephrol* 2006;17:2368–2382.
33. DuBose TD, Jr. Reclamation of filtered bicarbonate. *Kidney Int* 1990;38:584–589.
34. Bobulescu IA, Moe OW. Na^+/H^+ exchangers in renal regulation of acid-base balance. *Semin Nephrol* 2006;26:334–344.
35. Murer H, Hopfer U, Kinne R. Sodium/proton antiport in brush-border-membrane vesicles isolated from rat small intestine and kidney. *Biochem J* 1976;154:597–604.
36. Preisig PA, Ives HE, Cragge EJ, Jr, Alpern RJ, Rector FC, Jr. Role of the Na^+/H^+ antiporter in rat proximal tubule bicarbonate absorption. *J Clin Invest* 1987;80:970–978.
37. Zimolo Z, Montrose MH, Murer H. H^+extrusion by an apical vacuolar-type H^+-ATPase in rat renal proximal tubules. *J Membr Biol* 1992;126:19–26.
38. Breton S. The cellular physiology of carbonic anhydrases. *JOP* 2001;2:159–164.
39. Purkerson JM, Schwartz GJ. The role of carbonic anhydrases in renal physiology. *Kidney Int* 2007;71:103–115.
40. Schwartz GJ. Physiology and molecular biology of renal carbonic anhydrase. *J Nephrol* 2002;15(Suppl 5):S61–S74.
41. Boron WF, Boulpaep EL. The electrogenic Na/HCO_3 cotransporter. *Kidney Int* 1989;36:392–402.
42. Grassl SM, Aronson PS. Na^+/HCO_3^- co-transport in basolateral membrane vesicles isolated from rabbit renal cortex. *J Biol Chem* 1986;261:8778–8783.
43. Romero MF, Hediger MA, Boulpaep EL, Boron WF. Expression cloning and characterization of a renal electrogenic Na^+/HCO_3^- cotransporter. *Nature* 1997;387:409–413.
44. Pitts RF, Ayer JL, Schiess WA. The renal regulation of acid-base balance in man. III. The reabosrption and excretion of bicarbonate. *J Clin Invest* 1949;28:35–44.
45. Muto S, Asano Y, Okazaki H, Kano S. Renal potassium wasting in distal renal tubular acidosis: role of aldosterone. *Intern Med* 1992;31:1047–1051.
46. Pitts RF. Renal production and excretion of ammonia. *Am J Med* 1964;36:720–742.
47. Bank N, Schwartz WB. Influence of certain urinary solutes on acidic dissociation constant of ammonium at 37°C. *J Appl Physiol* 1960;15:125–127.
48. Curthoys NP. Renal ammonium ion production and excretion. In The Kidney: Physiology and Pathophysiology. Alpern RJ, Hebert SC (eds.). Burlington, MA, Elsevier, 2008, pp. 1601–1620.
49. DuBose TD, Jr, Good DW, Hamm LL, Wall SM. Ammonium transport in the kidney: New physiological concepts and their clinical implications. *J Am Soc Nephrol* 1991;1:1193–1203.
50. Karim Z, Szutkowska M, Vernimmen C, Bichara M. Renal handling of NH_3/NH_4^+: recent concepts. *Nephron Physiol* 2005;101:77–81.
51. Good DW, Knepper MA. Ammonia transport in the mammalian kidney. *Am J Physiol* 1985;248:F459–F471.
52. Curthoys NP, Gstraunthaler G. Mechanism of increased renal gene expression during metabolic acidosis. *Am J Physiol Renal Physiol* 2001;281:F381–F390.
53. Madison LL, Seldin DW. Ammonia excretion and renal enzymatic adaptation in human subjects, as disclosed by administration of precursor amino acids. *J Clin Invest* 1958;37:1615–1627.
54. Capasso G, Unwin R, Rizzo M, Pica A, Giebisch G. Bicarbonate transport along the loop of Henle: molecular mechanisms and regulation. *J Nephrol* 2002;15(Suppl 5):S88–S96.
55. Good DW, Knepper MA, Burg MB. Ammonia and bicarbonate transport by thick ascending limb of rat kidney. *Am J Physiol* 1984;247:F35–F44.
56. Breton S, Brown D. New insights into the regulation of V-ATPase-dependent proton secretion. *Am J Physiol Renal Physiol* 2007;292: F1–F10.
57. Karet FE. Physiological and metabolic implications of V-ATPase isoforms in the kidney. *J Bioenerg Biomembr* 2005;37:425–429.
58. Valles P, LaPointe MS, Wysocki J, Batlle D. Kidney vacuolar H^+-ATPase: physiology and regulation. *Semin Nephrol* 2006;26:361–374.
59. Wagner CA, Finberg KE, Breton S, Marshansky V, Brown D, Geibel JP. Renal vacuolar H^+-ATPase. *Physiol Rev* 2004;84:1263–1314.
60. Alper SL. Molecular physiology of SLC4 anion exchangers. *Exp Physiol* 2006;91:153–161.
61. Romero MF, Fulton CM, Boron WF. The SLC4 family of HCO_3^- transporters. *Pflugers Arch* 2004;447:495–509.
62. Boettger T, Hubner CA, Maier H, Rust MB, Beck FX, Jentsch TJ. Deafness and renal tubular acidosis in mice lacking the K-Cl co-transporter Kcc4. *Nature* 2002;416:874–878.
63. Kobayashi K, Uchida S, Mizutani S, Sasaki S, Marumo F. Intrarenal and cellular localization of CLC-K2 protein in the mouse kidney. *J Am Soc Nephrol* 2001;12:1327–1334.
64. Harrison HE. The Fanconi syndrome. *J Chronic Dis* 1958;7:346–355.
65. White PC, New MI, Dupont B. Congenital adrenal hyperplasia. (1). *N Engl J Med* 1987;316:1519–1524.
66. Quigley R. Proximal renal tubular acidosis. *J Nephrol* 2006;19 (Suppl 9):S41–S45.
67. Brenes LG, Brenes JN, Hernandez MM. Familial proximal renal tubular acidosis. A distinct clinical entity. *Am J Med* 1977; 63:244–252.
68. Nash MA, Torrado AD, Greifer I, Spitzer A, Edelmann CM, Jr. Renal tubular acidosis in infants and children. Clinical course, response to treatment, and prognosis. *J Pediatr* 1972;80:738–748.
69. Rodriguez-Soriano J, Vallo A, Castillo G, Oliveros R. Natural history of primary distal renal tubular acidosis treated since infancy. *J Pediatr* 1982;101:669–676.
70. Gil H, Santos F, Garcia E, Alvarez MV, Ordonez FA, Malaga S, Coto E. Distal RTA with nerve deafness: clinical spectrum and mutational analysis in five children. *Pediatr Nephrol* 2007; 22:825–828.
71. Brenes LG, Sanchez MI. Impaired urinary ammonium excretion in patients with isolated proximal renal tubular acidosis. *J Am Soc Nephrol* 1993;4:1073–1078.

72. Clarke BL, Wynne AG, Wilson DM, Fitzpatrick LA. Osteomalacia associated with adult Fanconi's syndrome: clinical and diagnostic features. *Clin Endocrinol (Oxf)* 1995;43:479–490.
73. Taylor HC, Elbadawy EH. Renal tubular acidosis type 2 with Fanconi's syndrome, osteomalacia, osteoporosis, and secondary hyperaldosteronism in an adult consequent to vitamin D and calcium deficiency: effect of vitamin D and calcium citrate therapy. *Endocr Pract* 2006;12:559–567.
74. Baum M. The Fanconi syndrome of cystinosis: insights into the pathophysiology. *Pediatr Nephrol* 1998;12:492–497.
75. Baum M. The cellular basis of Fanconi syndrome. *Hosp Pract (Off Ed)* 1993;28:137–138.
76. Gross P, Meye C. Proximal RTA: are all the charts completed yet? *Nephrol Dial Transplant* 2008;23:1101–1102.
77. Morris RC, Jr, McSherry E. Symposium on acid-base homeostasis. Renal acidosis. *Kidney Int* 1972;1:322–340.
78. Katzir Z, Dinour D, Reznik-Wolf H, Nissenkorn A, Holtzman E. Familial pure proximal renal tubular acidosis – a clinical and genetic study. *Nephrol Dial Transplant* 2008;23:1211–1215.
79. Igarashi T, Inatomi J, Sekine T, Cha SH, Kanai Y, Kunimi M, Tsukamoto K, Satoh H, Shimadzu M, Tozawa F, Mori T, Shiobara M, Seki G, Endou H. Mutations in SLC4A4 cause permanent isolated proximal renal tubular acidosis with ocular abnormalities. *Nat Genet* 1999;23:264–266.
80. Igarashi T, Sekine T, Inatomi J, Seki G. Unraveling the molecular pathogenesis of isolated proximal renal tubular acidosis. *J Am Soc Nephrol* 2002;13:2171–2177.
81. Pushkin A, Kurtz I. SLC4 base (HCO_3^- CO_3^{2-}) transporters: Classification, function, structure, genetic diseases, and knockout models. *Am J Physiol Renal Physiol* 2006;290:F580–F599.
82. Winsnes A, Monn E, Stokke O, Feyling T. Congenital persistent proximal type renal tubular acidosis in two brothers. *Acta Paediatr Scand* 1979;68:861–868.
83. Shiohara M, Igarashi T, Mori T, Komiyama A. Genetic and long-term data on a patient with permanent isolated proximal renal tubular acidosis. *Eur J Pediatr* 2000;159:892–894.
84. Igarashi T, Ishii T, Watanabe K, Hayakawa H, Horio K, Sone Y, Ohga K. Persistent isolated proximal renal tubular acidosis – a systemic disease with a distinct clinical entity. *Pediatr Nephrol* 1994;8:70–71.
85. Usui T, Hara M, Satoh H, Moriyama N, Kagaya H, Amano S, Oshika T, Ishii Y, Ibaraki N, Hara C, Kunimi M, Noiri E, Tsukamoto K, Inatomi J, Kawakami H, Endou H, Igarashi T, Goto A, Fujita T, Araie M, Seki G. Molecular basis of ocular abnormalities associated with proximal renal tubular acidosis. *J Clin Invest* 2001;108:107–115.
86. Bernardo AA, Bernardo CM, Espiritu DJ, Arruda JA. The sodium bicarbonate cotransporter: structure, function, and regulation. *Semin Nephrol* 2006;26:352–360.
87. Romero MF. Molecular pathophysiology of SLC4 bicarbonate transporters. *Curr Opin Nephrol Hypertens* 2005;14:495–501.
88. Soleimani M, Burnham CE. Na^+/HCO^{3-} cotransporters (NBC): cloning and characterization. *J Membr Biol* 2001;183:71–84.
89. Toye AM, Parker MD, Daly CM, Lu J, Virkki LV, Pelletier MF, Boron WF. The human NBCe1-A mutant R881C, associated with proximal renal tubular acidosis, retains function but is mistargeted in polarized renal epithelia. *Am J Physiol Cell Physiol* 2006;291: C788–C801.
90. Sly WS, Hewett-Emmett D, Whyte MP, Yu YS, Tashian RE. Carbonic anhydrase II deficiency identified as the primary defect in the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. *Proc Natl Acad Sci USA* 1983;80:2752–2756.
91. Schultheis PJ, Clarke LL, Meneton P, Miller ML, Soleimani M, Gawenis LR, Riddle TM, Duffy JJ, Doetschman T, Wang T, Giebisch G, Aronson PS, Lorenz JN, Shull GE. Renal and intestinal absorptive defects in mice lacking the NHE3 Na^+/H^+ exchanger. *Nat Genet* 1998;19:282–285.
92. Choi JY, Shah M, Lee MG, Schultheis PJ, Shull GE, Muallem S, Baum M. Novel amiloride-sensitive sodium-dependent proton secretion in the mouse proximal convoluted tubule. *J Clin Invest* 2000;105:1141–1146.
93. Warth R, Barriere H, Meneton P, Bloch M, Thomas J, Tauc M, Heitzmann D, Romeo E, Verrey F, Mengual R, Guy N, Bendahhou S, Lesage F, Poujeol P, Barhanin J. Proximal renal tubular acidosis in TASK2 K^+ channel-deficient mice reveals a mechanism for stabilizing bicarbonate transport. *Proc Natl Acad Sci USA* 2004;101:8215–8220.
94. Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med* 2002;347:111–121.
95. Kalatzis V, Antignac C. New aspects of the pathogenesis of cystinosis. *Pediatr Nephrol* 2003;18:207–215.
96. Kalatzis V, Antignac C. Cystinosis: from gene to disease. *Nephrol Dial Transplant* 2002;17:1883–1886.
97. Kalatzis V, Cherqui S, Antignac C, Gasnier B. Cystinosin, the protein defective in cystinosis, is a H^+-driven lysosomal cystine transporter. *EMBO J* 2001;20:5940–5949.
98. Fanconi G, Bickel H. Die chronische Aminoacidurie (AminosaÈ urediabetes oder nephrotisch-glukosurischer Zwerg-wuchs) bei der Glykogenose und der Cystinkrankheit. *Helv Paediatr Acta* 1949;4:359–396.
99. Santer R, Groth S, Kinner M, Dombrowski A, Berry GT, Brodehl J, Leonard JV, Moses S, Norgren S, Skovby F, Schneppenheim R, Steinmann B, Schaub J. The mutation spectrum of the facilitative glucose transporter gene SLC2A2 (GLUT2) in patients with Fanconi-Bickel syndrome. *Hum Genet* 2002;110:21–29.
100. Santer R, Schneppenheim R, Dombrowski A, Gotze H, Steinmann B, Schaub J. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. *Nat Genet* 1997;17:324–326.
101. Santer R, Schneppenheim R, Suter D, Schaub J, Steinmann B. Fanconi-Bickel syndrome – the original patient and his natural history, historical steps leading to the primary defect, and a review of the literature. *Eur J Pediatr* 1998;157:783–797.
102. Santer R, Steinmann B, Schaub J. Fanconi-Bickel syndrome – a congenital defect of facilitative glucose transport. *Curr Mol Med* 2002;2:213–227.
103. Morris RC, Jr. An experimental renal acidification defect in patients with hereditary fructose intolerance. II. Its distinction from classic renal tubular acidosis; its resemblance to the renal acidification defect associated with the Fanconi syndrome of children with cystinosis. *J Clin Invest* 1968;47:1648–1663.
104. Morris RC, Jr. An experimental renal acidification defect in patients with hereditary fructose intolerance. I. Its resemblance to renal tubular acidosis. *J Clin Invest* 1968;47:1389–1398.
105. Zhang X, Jefferson AB, Auethavekiat V, Majerus PW. The protein deficient in Lowe syndrome is a phosphatidylinositol-4, 5-bisphosphate 5-phosphatase. *Proc Natl Acad Sci USA* 1995;92:4853–4856.

106. Suchy SF, Nussbaum RL. The deficiency of PIP2 5-phosphatase in Lowe syndrome affects actin polymerization. *Am J Hum Genet* 2002;71:1420–1427.
107. Devuyst O, Jouret F, Auzanneau C, Courtoy PJ. Chloride channels and endocytosis: new insights from Dent's disease and ClC-5 knockout mice. *Nephron Physiol* 2005;99:69–73.
108. Hryciw DH, Ekberg J, Pollock CA, Poronnik P. ClC-5: a chloride channel with multiple roles in renal tubular albumin uptake. *Int J Biochem Cell Biol* 2006;38:1036–1042.
109. Lloyd SE, Pearce SH, Fisher SE, Steinmeyer K, Schwappach B, Scheinman SJ, Harding B, Bolino A, Devoto M, Goodyer P, Rigden SP, Wrong O, Jentsch TJ, Craig IW, Thakker RV. A common molecular basis for three inherited kidney stone diseases. *Nature* 1996;379:445–449.
110. Wang SS, Devuyst O, Courtoy PJ, Wang XT, Wang H, Wang Y, Thakker RV, Guggino S, Guggino WB. Mice lacking renal chloride channel, CLC-5, are a model for Dent's disease, a nephrolithiasis disorder associated with defective receptor-mediated endocytosis. *Hum Mol Genet* 2000;9:2937–2945.
111. Aperia A, Bergqvist G, Linne T, Zetterstrom R. Familial Fanconi syndrome with malabsorption and galactose intolerance, normal kinase and transferase activity. A report on two siblings. *Acta Paediatr Scand* 1981;70:527–533.
112. Endo F, Sun MS. Tyrosinaemia type I and apoptosis of hepatocytes and renal tubular cells. *J Inherit Metab Dis* 2002;25:227–234.
113. Kubo S, Sun M, Miyahara M, Umeyama K, Urakami K, Yamamoto T, Jakobs C, Matsuda I, Endo F. Hepatocyte injury in tyrosinemia type 1 is induced by fumarylacetoacetate and is inhibited by caspase inhibitors. *Proc Natl Acad Sci USA* 1998;95:9552–9557.
114. Sun MS, Hattori S, Kubo S, Awata H, Matsuda I, Endo F. A mouse model of renal tubular injury of tyrosinemia type 1: development of De Toni Fanconi syndrome and apoptosis of renal tubular cells in Fah/Hpd double mutant mice. *J Am Soc Nephrol* 2000;11:291–300.
115. Chen YT. Type I glycogen storage disease: Kidney involvement, pathogenesis and its treatment. *Pediatr Nephrol* 1991;5:71–76.
116. Chen YT, Coleman RA, Scheinman JI, Kolbeck PC, Sidbury JB. Renal disease in type I glycogen storage disease. *N Engl J Med* 1988;318:7–11.
117. Ozen H. Glycogen storage diseases: new perspectives. *World J Gastroenterol* 2007;13:2541–2553.
118. Niaudet P, Heidet L, Munnich A, Schmitz J, Bouissou F, Gubler MC, Rotig A. Deletion of the mitochondrial DNA in a case of De Toni-Debre-Fanconi syndrome and Pearson syndrome. *Pediatr Nephrol* 1994;8:164–168.
119. Niaudet P, Rotig A. Renal involvement in mitochondrial cytopathies. *Pediatr Nephrol* 1996;10:368–373.
120. Niaudet P, Rotig A. The kidney in mitochondrial cytopathies. *Kidney Int* 1997;51:1000–1007.
121. Rotig A. Renal disease and mitochondrial genetics. *J Nephrol* 2003;16:286–292.
122. Pontoglio M, Barra J, Hadchouel M, Doyen A, Kress C, Bach JP, Babinet C, Yaniv M. Hepatocyte nuclear factor 1 inactivation results in hepatic dysfunction, phenylketonuria, and renal Fanconi syndrome. *Cell* 1996;84:575–585.
123. Pontoglio M. Hepatocyte nuclear factor 1, a transcription factor at the crossroads of glucose homeostasis. *J Am Soc Nephrol* 2000;11 (Suppl 16):S140–S143.
124. Pontoglio M, Prie D, Cheret C, Doyen A, Leroy C, Froguel P, Velho G, Yaniv M, Friedlander G. HNF1alpha controls renal glucose reabsorption in mouse and man. *EMBO Rep* 2000;1:359–365.
125. Supuran CT, Scozzafava A, Casini A. Carbonic anhydrase inhibitors. *Med Res Rev* 2003;23:146–189.
126. Guerrini R, Parmeggiani L. Topiramate and its clinical applications in epilepsy. *Expert Opin Pharmacother* 2006;7:811–823.
127. Perucca E. A pharmacological and clinical review on topiramate, a new antiepileptic drug. *Pharmacol Res* 1997;35:241–256.
128. Supuran CT. Carbonic anhydrases as drug targets. *Curr Pharm Des* 2008;14:601–602.
129. Supuran CT. Carbonic anhydrases – an overview. *Curr Pharm Des* 2008;14:603–614.
130. Barbier O, Jacquillet G, Tauc M, Cougnon M, Poujeol P. Effect of heavy metals on, and handling by, the kidney. *Nephron Physiol* 2005;99:105–110.
131. Choudhury D, Ahmed Z. Drug-induced nephrotoxicity. *Med Clin North Am* 1997;81:705–717.
132. Choudhury D, Ahmed Z. Drug-associated renal dysfunction and injury. *Nat Clin Pract Nephrol* 2006;2:80–91.
133. Izzedine H, Launay-Vacher V, Isnard-Bagnis C, Deray G. Drug-induced Fanconi's syndrome. *Am J Kidney Dis* 2003;41:292–309.
134. Lande MB, Kim MS, Bartlett C, Guay-Woodford LM. Reversible Fanconi syndrome associated with valproate therapy. *J Pediatr* 1993;123:320–322.
135. Zaki EL, Springate JE. Renal injury from valproic acid: case report and literature review. *Pediatr Neurol* 2002;27:318–319.
136. Izumotani T, Ishimura E, Tsumura K, Goto K, Nishizawa Y, Morii H. An adult case of Fanconi syndrome due to a mixture of Chinese crude drugs. *Nephron* 1993;65:137–140.
137. Lee S, Lee T, Lee B, Choi H, Yang M, Ihm CG, Kim M. Fanconi's syndrome and subsequent progressive renal failure caused by a Chinese herb containing aristolochic acid. *Nephrology (Carlton)* 2004;9:126–129.
138. Ghiculescu RA, Kubler PA. Aminoglycoside-associated Fanconi syndrome. *Am J Kidney Dis* 2006;48:e89–e93.
139. James CW, Steinhaus MC, Szabo S, Dressier RM. Tenofovir-related nephrotoxicity: case report and review of the literature. *Pharmacotherapy* 2004;24:415–418.
140. Melnick JZ, Baum M, Thompson JR. Aminoglycoside-induced Fanconi's syndrome. *Am J Kidney Dis* 1994;23:118–122.
141. Quimby D, Brito MO. Fanconi syndrome associated with use of tenofovir in HIV-infected patients: a case report and review of the literature. *AIDS Read* 2005;15:357–364.
142. Rossi R, Pleyer J, Schafers P, Kuhn N, Kleta R, Deufel T, Jurgens H. Development of ifosfamide-induced nephrotoxicity: prospective follow-up in 75 patients. *Med Pediatr Oncol* 1999;32:177–182.
143. Skinner R. Chronic ifosfamide nephrotoxicity in children. *Med Pediatr Oncol* 2003;41:190–197.
144. Skinner R, Pearson AD, Craft AW. Ifosfamide nephrotoxicity in children. *Med Pediatr Oncol* 1994;22:153–154.
145. Tsimihodimos V, Psychogios N, Kakaidi V, Bairaktari E, Elisaf M. Salicylate-induced proximal tubular dysfunction. *Am J Kidney Dis* 2007;50:463–467.
146. Pessler F, Emery H, Dai L, Wu YM, Monash B, Cron RQ, Pradhan M. The spectrum of renal tubular acidosis in paediatric Sjogren syndrome. *Rheumatology (Oxford)* 2006;45:85–91.
147. Decourt C, Bridoux F, Touchard G, Cogne M. A monoclonal V kappa l light chain responsible for incomplete proximal tubulopathy. *Am J Kidney Dis* 2003;41:497–504.
148. Lacy MQ, Gertz MA. Acquired Fanconi's syndrome associated with monoclonal gammopathies. *Hematol Oncol Clin North Am* 1999;13:1273–1280.

149. Messiaen T, Deret S, Mougenot B, Bridoux F, Dequiedt P, Dion JJ, Makdassi R, Meeus F, Pourrat J, Touchard G, Vanhille P, Zaoui P, Aucouturier P, Ronco PM. Adult Fanconi syndrome secondary to light chain gammopathy. Clinicopathologic heterogeneity and unusual features in 11 patients. *Medicine (Baltimore)* 2000; 79:135–154.
150. Guignard JP, Torrado A. Proximal renal tubular acidosis in vitamin D deficiency rickets. *Acta Paediatr Scand* 1973;62:543–546.
151. Vainsel M, Manderlier T, Vis HL. Proximal renal tubular acidosis in vitamin D deficiency rickets. *Biomedicine* 1975;22:35–40.
152. Firmin CJ, Kruger TF, Davids R. Proximal renal tubular acidosis in pregnancy. A case report and literature review. *Gynecol Obstet Invest* 2007;63:39–44.
153. Riley AL, Ryan LM, Roth DA. Renal proximal tubular dysfunction and paroxysmal nocturnal hemoglobinuria. *Am J Med* 1977; 62:125–129.
154. Brodwall EK, Westlie L, Myhre E. The renal excretion and tubular reabsorption of citric acid in renal tubular acidosis. *Acta Med Scand* 1972;192:137–139.
155. Simpson DP. Citrate excretion: a window on renal metabolism. *Am J Physiol* 1983;244:F223–F234.
156. Borthwick KJ, Kandemir N, Topaloglu R, Kornak U, Bakkaloglu A, Yordam N, Ozen S, Mocan H, Shah GN, Sly WS, Karet FE. A phenocopy of CAII deficiency: a novel genetic explanation for inherited infantile osteopetrosis with distal renal tubular acidosis. *J Med Genet* 2003;40:115–121.
157. Serrano A, Batlle D. Images in clinical medicine. Bilateral kidney calcifications. *N Engl J Med* 2008;359:e1.
158. Feest TG, Proctor S, Brown R, Wrong OM. Nephrocalcinosis: another cause of renal erythrocytosis. *Br Med J* 1978;2:605.
159. Feest TG, Wrong O. Erythrocytosis and nephrocalcinosis. *Nephrol Dial Transplant* 1992;7:1071.
160. Kamel KS, Briceno LF, Sanchez MI, Brenes L, Yorgin P, Kooh SW, Balfe JW, Halperin ML. A new classification for renal defects in net acid excretion. *Am J Kidney Dis* 1997;29:136–146.
161. Miller SG, Schwartz GJ. Hyperammonaemia with distal renal tubular acidosis. *Arch Dis Child* 1997;77:441–444.
162. Pela I, Seracini D. Hyperammonemia in distal renal tubular acidosis: is it more common than we think? *Clin Nephrol* 2007; 68:109–114.
163. Seracini D, Poggi GM, Pela I. Hyperammonaemia in a child with distal renal tubular acidosis. *Pediatr Nephrol* 2005; 20:1645–1647.
164. Batlle D, Moorthi KM, Schlueter W, Kurtzman N. Distal renal tubular acidosis and the potassium enigma. *Semin Nephrol* 2006;26:471–478.
165. Sebastian A, McSherry E, Morris RC, Jr. Renal potassium wasting in renal tubular acidosis (RTA): its occurrence in types 1 and 2 RTA despite sustained correction of systemic acidosis. *J Clin Invest* 1971;50:667–678.
166. Bresolin NL, Grillo E, Fernandes VR, Carvalho FL, Goes JE, DaSilva RJ. A case report and review of hypokalemic paralysis secondary to renal tubular acidosis. *Pediatr Nephrol* 2005; 20:818–820.
167. Siamopoulos KC, Elisaf M, Moutsopoulos HM. Hypokalaemic paralysis as the presenting manifestation of primary Sjogren's syndrome. *Nephrol Dial Transplant* 1994;9:1176–1178.
168. Gallagher PG. Red cell membrane disorders. *Hematology Am Soc Hematol Educ Program.* 2005;13–18.
169. Tanner MJ. The structure and function of band 3 (AE1): recent developments (review). *Mol Membr Biol* 1997;14:155–165.
170. Bruce LJ, Cope DL, Jones GK, Schofield AE, Burley M, Povey S, Unwin RJ, Wrong O, Tanner MJ. Familial distal renal tubular acidosis is associated with mutations in the red cell anion exchanger (Band 3, AE1) gene. *J Clin Invest* 1997;100:1693–1707.
171. Karet FE, Gainza FJ, Gyory AZ, Unwin RJ, Wrong O, Tanner MJ, Nayir A, Alpay H, Santos F, Hulton SA, Bakkaloglu A, Ozen S, Cunningham MJ, Di Pietro A, Walker WG, Lifton RP. Mutations in the chloride-bicarbonate exchanger gene AE1 cause autosomal dominant but not autosomal recessive distal renal tubular acidosis. *Proc Natl Acad Sci USA* 1998;95:6337–6342.
172. Fry AC, Karet FE. Inherited renal acidoses. *Physiology (Bethesda)* 2007;22:202–211.
173. Karet FE. Inherited distal renal tubular acidosis. *J Am Soc Nephrol* 2002;13:2178–2184.
174. Khositseth S, Sirikanaerat A, Khoprasert S, Opastirakul S, Kingwatanakul P, Thongnoppakhun W, Yenchitsomanus PT. Hematological abnormalities in patients with distal renal tubular acidosis and hemoglobinopathies. *Am J Hematol* 2008;83:465–471.
175. Wrong O, Bruce LJ, Unwin RJ, Toye AM, Tanner MJ. Band 3 mutations, distal renal tubular acidosis, and Southeast Asian ovalocytosis. *Kidney Int* 2002;62:10–19.
176. Yenchitsomanus PT. Human anion exchanger1 mutations and distal renal tubular acidosis. *Southeast Asian J Trop Med Public Health* 2003;34:651–658.
177. Karet FE, Finberg KE, Nelson RD, Nayir A, Mocan H, Sanjad SA, Rodriguez-Soriano J, Santos F, Cremers CW, Di Pietro A, Hoffbrand BI, Winiarski J, Bakkaloglu A, Ozen S, Dusunsel R, Goodyer P, Hulton SA, Wu DK, Skvorak AB, Morton CC, Cunningham MJ, Jha V, Lifton RP. Mutations in the gene encoding B1 subunit of H^+-ATPase cause renal tubular acidosis with sensory neural deafness. *Nat Genet* 1999;21:84–90.
178. Lang F, Vallon V, Knipper M, Wangemann P. Functional significance of channels and transporters expressed in the inner ear and kidney. *Am J Physiol Cell Physiol* 2007;293:C1187–C1208.
179. Peters TA, Monnens LA, Cremers CW, Curfs JH. Genetic disorders of transporters/channels in the inner ear and their relation to the kidney. *Pediatr Nephrol* 2004;19:1194–1201.
180. Stover EH, Borthwick KJ, Bavalia C, Eady N, Fritz DM, Rungroj N, Giersch AB, Morton CC, Axon PR, Akil I, Al-Sabban EA, Baguley DM, Bianca S, Bakkaloglu A, Bircan Z, Chauveau D, Clermont MJ, Guala A, Hulton SA, Kroes H, Li VG, Mir S, Mocan H, Nayir A, Ozen S, Rodriguez SJ, Sanjad SA, Tasic V, Taylor CM, Topaloglu R, Smith AN, Karet FE. Novel ATP6V1B1 and ATP6V0A4 mutations in autosomal recessive distal renal tubular acidosis with new evidence for hearing loss. *J Med Genet* 2002;39:796–803.
181. Bajaj G, Quan A. Renal tubular acidosis and deafness: report of a large family. *Am J Kidney Dis* 1996;27:880–882.
182. Fuster DG, Zhang J, Xie XS, Moe OW. The vacuolar-ATPase B1 subunit in distal tubular acidosis: novel mutations and mechanisms for dysfunction. *Kidney Int* 2008;73:1151–1158.
183. Smith AN, Skaug J, Choate KA, Nayir A, Bakkaloglu A, Ozen S, Hulton SA, Sanjad SA, Al Sabban EA, Lifton RP, Scherer SW, Karet FE. Mutations in ATP6N1B, encoding a new kidney vacuolar proton pump 116-kD subunit, cause recessive distal renal tubular acidosis with preserved hearing. *Nat Genet* 2000;26:71–75.
184. Stehberger PA, Shmukler BE, Stuart-Tilley AK, Peters LL, Alper SL, Wagner CA. Distal renal tubular acidosis in mice lacking the AE1 (band3) Cl^-/HCO_3^- exchanger (slc4a1). *J Am Soc Nephrol* 2007;18:1408–1418.
185. Blomqvist SR, Vidarsson H, Fitzgerald S, Johansson BR, Ollerstam A, Brown R, Persson AE, Bergstrom GG, Enerback S.

Distal renal tubular acidosis in mice that lack the forkhead transcription factor Foxi1. *J Clin Invest* 2004;113:1560–1570.
186. Cohen EP, Bastani B, Cohen MR, Kolner S, Hemken P, Gluck SL. Absence of H^+-ATPase in cortical collecting tubules of a patient with Sjogren's syndrome and distal renal tubular acidosis. *J Am Soc Nephrol* 1992;3:264–271.
187. Pertovaara M, Korpela M, Kouri T, Pasternack A. The occurrence of renal involvement in primary Sjogren's syndrome: a study of 78 patients. *Rheumatology (Oxford)* 1999;38:1113–1120.
188. Siamopoulos KC, Elisaf M, Drosos AA, Mavridis AA, Moutsopoulos HM. Renal tubular acidosis in primary Sjogren's syndrome. *Clin Rheumatol* 1992;11:226–230.
189. Bagga A, Jain Y, Srivastava RN, Bhuyan UN. Renal tubular acidosis preceding systemic lupus erythematosus. *Pediatr Nephrol* 1993; 7:735–736.
190. Caruana RJ, Barish CF, Buckalew VM, Jr. Complete distal renal tubular acidosis in systemic lupus: clinical and laboratory findings. *Am J Kidney Dis* 1985;6:59–63.
191. Konishi K, Hayashi M, Saruta T. Renal tubular acidosis with autoantibody directed to renal collecting-duct cells. *N Engl J Med* 1994;331:1593–1594.
192. Li SL, Liou LB, Fang JT, Tsai WP. Symptomatic renal tubular acidosis (RTA) in patients with systemic lupus erythematosus: an analysis of six cases with new association of type 4 RTA. *Rheumatology (Oxford)* 2005;44:1176–1180.
193. Schwarz C, Benesch T, Kodras K, Oberbauer R, Haas M. Complete renal tubular acidosis late after kidney transplantation. *Nephrol Dial Transplant* 2006;21:2615–2620.
194. McCurdy DK, Frederic M, Elkinton JR. Renal tubular acidosis due to amphotericin B. *N Engl J Med* 1968;278:124–130.
195. Roscoe JM, Goldstein MB, Halperin ML, Schloeder FX, Stinebaugh BJ. Effect of amphotercin B on urine acidification in rats: Implications for the pathogenesis of distal renal tubular acidosis. *J Lab Clin Med* 1977;89:463–470.
196. Stinebaugh BJ, Schloeder FX, Tam SC, Goldstein MB, Halperin ML. Pathogenesis of distal renal tubular acidosis. *Kidney Int* 1981;19:1–7.
197. Hoorn EJ, Zietse R. Combined renal tubular acidosis and diabetes insipidus in hematological disease. *Nat Clin Pract Nephrol* 2007;3:171–175.
198. Navarro JF, Quereda C, Quereda C, Gallego N, Antela A, Mora C, Ortuno J. Nephrogenic diabetes insipidus and renal tubular acidosis secondary to foscarnet therapy. *Am J Kidney Dis* 1996;27:431–434.
199. Roscoe JM, Goldstein MB, Halperin ML, Wilson DR, Stinebaugh BJ. Lithium-induced impairment of urine acidification. *Kidney Int* 1976;9:344–350.
200. Seikaly M, Browne R, Baum M. Nephrocalcinosis is associated with renal tubular acidosis in children with X-linked hypophosphatemia. *Pediatrics* 1996;97:91–93.
201. Bonilla-Felix M, Villegas-Medina O, Vehaskari VM. Renal acidification in children with idiopathic hypercalciuria. *J Pediatr* 1994;124:529–534.
202. Nilwarangkur S, Nimmannit S, Chaovakul V, Susaengrat W, Ong-aj-yooth S, Vasuvattakul S, Pidetcha P, Malasit P. Endemic primary distal renal tubular acidosis in Thailand. *Q J Med* 1990;74:289–301.
203. Dafnis E, Spohn M, Lonis B, Kurtzman NA, Sabatini S. Vanadate causes hypokalemic distal renal tubular acidosis. *Am J Physiol* 1992;262:F449–F453.
204. Carlisle EJ, Donnelly SM, Vasuvattakul S, Kamel KS, Tobe S, Halperin ML. Glue-sniffing and distal renal tubular acidosis: sticking to the facts. *J Am Soc Nephrol* 1991;1:1019–1027.
205. Vainsel M, Fondu P, Cadranel S, Rocmans C, Gepts W. Osteopetrosis associated with proximal and distal tubular acidosis. *Acta Paediatr Scand* 1972;61:429–434.
206. Nagai R, Kooh SW, Balfe JW, Fenton T, Halperin ML. Renal tubular acidosis and osteopetrosis with carbonic anhydrase II deficiency: pathogenesis of impaired acidification. *Pediatr Nephrol* 1997;11:633–636.
207. Sly WS, Whyte MP, Sundaram V, Tashian RE, Hewett-Emmett D, Guibaud P, Vainsel M, Baluarte HJ, Gruskin A, Al-Mosawi M. Carbonic anhydrase II deficiency in 12 families with the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. *N Engl J Med* 1985;313:139–145.
208. Del FA, Cappariello A, Teti A. Genetics, pathogenesis and complications of osteopetrosis. *Bone* 2008;42:19–29.
209. Wagner CA, Geibel JP. Acid-base transport in the collecting duct. *J Nephrol* 2002;15(Suppl 5):S112–S127.
210. Sartorius OW, Calhoon D, Pitts RF. The capacity of the adrenalectomized rat to secrete hydrogen and ammonium ions. *Endocrinology* 1952;51:444–450.
211. Sartorius OW, Calhoon D, Pitts RF. Studies on the interrelationships of the adrenal cortex and renal ammonia excretion by the rat. *Endocrinology* 1953;52:256–265.
212. Welbourne TC, Francoeur D. Influence of aldosterone on renal ammonia production. *Am J Physiol* 1977;233:E56–E60.
213. DuBose TD, Jr. Hyperkalemic hyperchloremic metabolic acidosis: pathophysiologic insights. *Kidney Int* 1997;51:591–602.
214. DuBose TD, Jr. Molecular and pathophysiologic mechanisms of hyperkalemic metabolic acidosis. *Trans Am Clin Climatol Assoc* 2000;111:122–133.
215. White PC, New MI, Dupont B. Congenital adrenal hyperplasia (2). *N Engl J Med* 1987;316:1580–1586.
216. White PC. Steroid 11 beta-hydroxylase deficiency and related disorders. *Endocrinol Metab Clin North Am* 2001;30:61–79, vi.
217. Geller DS, Rodriguez-Soriano J, Vallo BA, Schifter S, Bayer M, Chang SS, Lifton RP. Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism type I. *Nat Genet* 1998;19:279–281.
218. Chang SS, Grunder S, Hanukoglu A, Rosler A, Mathew PM, Hanukoglu I, Schild L, Lu Y, Shimkets RA, Nelson-Williams C, Rossier BC, Lifton RP. Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. *Nat Genet* 1996;12:248–253.
219. Gordon RD. Syndrome of hypertension and hyperkalemia with normal glomerular filtration rate. *Hypertension* 1986;8:93–102.
220. Schambelan M, Sebastian A, Rector FC, Jr. Mineralocorticoid-resistant renal hyperkalemia without salt wasting (type II pseudohypoaldosteronism): role of increased renal chloride reabsorption. *Kidney Int* 1981;19:716–727.
221. Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, Gunel M, Milford DV, Lipkin GW, Achard JM, Feely MP, Dussol B, Berland Y, Unwin RJ, Mayan H, Simon DB, Farfel Z, Jeunemaitre X, Lifton RP. Human hypertension caused by mutations in WNK kinases. *Science* 2001; 293:1107–1112.
222. Knochel JP. The syndrome of hyporeninemic hypoaldosteronism. *Annu Rev Med* 1979;30:145–153.

223. Sebastian A, Schambelan M, Lindenfeld S, Morris RC, Jr. Amelioration of metabolic acidosis with fludrocortisone therapy in hyporeninemic hypoaldosteronism. *N Engl J Med* 1977;297:576–583.
224. Kristjansson K, Laxdal T, Ragnarsson J. Type 4 renal tubular acidosis (sub-type 2) associated with idiopathic interstitial nephritis. *Acta Paediatr Scand* 1986;75:1051–1054.
225. Keven K, Ozturk R, Sengul S, Kutlay S, Ergun I, Erturk S, Erbay B. Renal tubular acidosis after kidney transplantation – incidence, risk factors and clinical implications. *Nephrol Dial Transplant* 2007;22:906–910.
226. Olyaei AJ, DeMattos AM, Bennett WM. Immunosuppressant-induced nephropathy: Pathophysiology, incidence and management. *Drug Saf* 1999;21:471–488.
227. Bagga A, Bajpai A, Menon S. Approach to renal tubular disorders. *Indian J Pediatr* 2005;72:771–776.
228. Bagga A, Sinha A. Evaluation of renal tubular acidosis. *Indian J Pediatr* 2007;74:679–686.
229. Rodriguez SJ. Renal tubular acidosis: the clinical entity. *J Am Soc Nephrol* 2002;13:2160–2170.
230. Rodriguez-Soriano J, Vallo A. Renal tubular acidosis. *Pediatr Nephrol* 1990;4:268–275.
231. Adedoyin O, Gottlieb B, Frank R, Vento S, Vergara M, Gauthier B, Trachtman H. Evaluation of failure to thrive: diagnostic yield of testing for renal tubular acidosis. *Pediatrics* 2003;112:e463.
232. Emmett M, Narins RG. Clinical use of the anion gap. *Medicine (Baltimore)* 1977;56:38–54.
233. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol* 2007;2:162–174.
234. Oh MS, Carroll HJ. The anion gap. *N Engl J Med* 1977;297:814–817.
235. Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. *N Engl J Med* 1988;318:594–599.
236. Dyck RF, Asthana S, Kalra J, West ML, Massey KL. A modification of the urine osmolal gap: An improved method for estimating urine ammonium. *Am J Nephrol* 1990;10:359–362.
237. Goldstein MB, Bear R, Richardson RM, Marsden PA, Halperin ML. The urine anion gap: a clinically useful index of ammonium excretion. *Am J Med Sci* 1986;292:198–202.
238. Halperin ML, Margolis BL, Robinson LA, Halperin RM, West ML, Bear RA. The urine osmolal gap: a clue to estimate urine ammonium in "hybrid" types of metabolic acidosis. *Clin Invest Med* 1988;11:198–202.
239. Kim GH, Han JS, Kim YS, Joo KW, Kim S, Lee JS. Evaluation of urine acidification by urine anion gap and urine osmolal gap in chronic metabolic acidosis. *Am J Kidney Dis* 1996;27:42–47.
240. Richardson RM, Halperin ML. The urine pH: a potentially misleading diagnostic test in patients with hyperchloremic metabolic acidosis. *Am J Kidney Dis* 1987;10:140–143.
241. Kleta R, Gahl WA. Pharmacological treatment of nephropathic cystinosis with cysteamine. *Expert Opin Pharmacother* 2004; 5:2255–2262.
242. Kirschbaum B, Sica D, Anderson FP. Urine electrolytes and the urine anion and osmolar gaps. *J Lab Clin Med* 1999;133:597–604.
243. Sulyok E, Guignard JP. Relationship of urinary anion gap to urinary ammonium excretion in the neonate. *Biol Neonate* 1990; 57:98–106.
244. DuBose TD, Jr, Caflisch CR. Validation of the difference in urine and blood carbon dioxide tension during bicarbonate loading as an index of distal nephron acidification in experimental models of distal renal tubular acidosis. *J Clin Invest* 1985;75:1116–1123.
245. Kim S, Lee JW, Park J, Na KY, Joo KW, Ahn C, Kim S, Lee JS, Kim GH, Kim J, Han JS. The urine-blood PCO gradient as a diagnostic index of H^+-ATPase defect distal renal tubular acidosis. *Kidney Int* 2004;66:761–767.
246. Lin JY, Lin JS, Tsai CH. Use of the urine-to-blood carbon dioxide tension gradient as a measurement of impaired distal tubular hydrogen ion secretion among neonates. *J Pediatr* 1995;126:114–117.
247. Walsh SB, Shirley DG, Wrong OM, Unwin RJ. Urinary acidification assessed by simultaneous furosemide and fludrocortisone treatment: an alternative to ammonium chloride. *Kidney Int* 2007; 71:1310–1316.
248. Kleta R, Bernardini I, Ueda M, Varade WS, Phornphutkul C, Krasnewich D, Gahl WA. Long-term follow-up of well-treated nephropathic cystinosis patients. *J Pediatr* 2004;145:555–560.
249. Schneider JA. Treatment of cystinosis: simple in principle, difficult in practice. *J Pediatr* 2004;145:436–438.
250. Domrongkitchaiporn S, Khositseth S, Stitchantrakul W, Tapaneya-Olarn W, Radinahamed P. Dosage of potassium citrate in the correction of urinary abnormalities in pediatric distal renal tubular acidosis patients. *Am J Kidney Dis* 2002;39:383–391.
251. Tapaneya-Olarn W, Khositseth S, Tapaneya-Olarn C, Teerakarnjana N, Chaichanajarernkul U, Stitchantrakul W, Petchthong T. The optimal dose of potassium citrate in the treatment of children with distal renal tubular acidosis. *J Med Assoc Thai* 2002;854:S1143–S1149.
252. Morris RC, Jr, Sebastian A. Alkali therapy in renal tubular acidosis: who needs it? *J Am Soc Nephrol* 2002;13:2186–2188.