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REVIEW ARTICLE

Renal tubular acidosis in children: state of the art, diagnosis and treatment

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ABSTRACT

Overdiagnosis of renal tubular acidosis (RTA) has been recently detected in Mexican children, perhaps due to diagnostic errors as well as due to a lack of knowledge regarding the pathophysiology and molecular biochemistry involved in this illness. The objective of the present study is to facilitate the knowledge and diagnosis of RTA, a clinical condition infrequently seen worldwide. RTA is an alteration of the acid-base equilibrium due to a bicarbonate wasting in the proximal renal tubules [proximal RTA, (pRTA) or type 2 RTA] or due to a distal nephron hydrogen ion excretion defect [distal RTA (dRTA) or type 1 RTA]. Hyperkalemic, or type 4 RTA, is due to alterations in aldosterone metabolism. RTA may be primary, secondary, acquired or hereditary and frequently presents secondary to an array of systemic diseases, usually accompanied by multiple renal tubular defects. The main defect occurs in the transmembrane transporters such as carbonic anhydrase (CA I and II), H^+-ATPase, HCO_3^-/Cl^- (AE1) exchanger and Na^+/HCO_3^- (NBCe1) cotransporter.

Diagnosis should include the presence of hyperchloremic metabolic acidosis with normal serum anion gap (done in an arterial or arterialized blood sample), lack of appetite, polyuria, thirst, growth failure, and rickets; nephrocalcinosis and renal stones (in dRTA); abnormal urine anion gap and abnormal urine/serum pCO_2 gradient. Diagnosis of a primary systemic disease must be made in cases of secondary RTA.

Bicarbonate or potassium citrate therapy as well as potassium, calcium and vitamin D administration depends on the type and severity of the RTA.

Key words: acidosis, renal tubular acidosis, transmembrane transporters.

INTRODUCTION

Renal tubular acidosis (RTA) is pathophysiological disorder of acid-base metabolism characterized by the presence of hyperchloremic metabolic acidosis caused by renal loss of bicarbonate or by reduced renal tubular excretion of hydrogen ions.[1] In Mexico the incidence of RTA is unknown, mainly due to the lack of recording of renal diseases. García de la Puente reported a prevalence of 35 cases/10,000 in the Instituto Nacional de Pediatría (INP).[2] However, the diagnostic methodology is not mentioned and biochemical parameters of patients are not shown.

In Spain, with a population of 45 million, only 50 cases of hereditary RTA in the renal tubule have been reported and of these only 20 are Spaniards.[3] In most European countries, the incidence is also rare. Genetic studies estimate a ratio of ~1 case/million population in the UK and France.[4-6] The population with distal RTA (dRTA) is concentrated on immigrants of Arabic origin. Although RTA is a rare alteration worldwide, in recent years an alarming rate of over-diagnosis has occurred in Mexico.[7] This is likely due to errors in interpretation of the pathophysiology involved in the different types of RTA and lack of detection of the primary disease causing the RTA, as well as diagnostic errors.

The aim of this article is to report the classification, pathophysiology, management and treatment of this renal disorder so as to guide pediatricians and other specialists on the physiological basis and complicated biochemical processes involved in this alteration of acid-base metabolism.

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Under physiological conditions, the extracellular space is maintained at an alkaline pH with a narrow gap, pH 7.40 ± 0.5, indicating a low presence of free hydrogen ions ([H+]: ($[H^+]$) 0.0000000398 mmol/l) despite the large amounts of hydrogen ions produced daily in the organism as a result of the ability of the kidneys to eliminate them. The principal source of organic H^+ production is derived from dietary protein and hence the metabolism of amino acids, particularly leucine, isoleucine, methionine and lysine, as well as the formation of hydroxyapatite from calcium and phosphate deposits for bone growth in children. Hydrogen ion production in adults is 60-100 mmol/day, on average 1 mmol/kg body weight, whereas in children it is 2-3 mmol/kg/day. In order to achieve an acid-base balance, elimination of hydrogen ions must equal the rate of production, which occurs during fine regulation in the collecting tubules. For the kidneys to excrete large amounts of hydrogen ions in their free form would require reducing urinary pH to 1.5, which does not happen because it would cause irreparable damage to urinary tract tissues. However, under physiological conditions, the urine maintains a stable acidic pH (5.5-6.5) because free hydrogen ions bind to buffer ammonia molecules (NH_3) to later form ammonia (NH_4^+) to be excreted by this route. Also, free hydrogen ions bind to phosphates (to form phosphoric acid) and sulfates (to form sulfuric acid). Measurement of the latter two in the urine is called titratable acidity.

CLASSIFICATION

RTA classification has undergone changes over time and currently is called type 1 RTA or dRTA when excretion of hydrogen ion does not occur and, therefore, renal tubular reabsorption of HCO_3. The defect is located in the connector, the initial collector, the cortical collector and external medullary tubules. Type 2 RTA is characterized by a reduction in the reabsorption of bicarbonate (HCO_3^-) in the proximal tubule (pRTA).[8] The classification is confusing because according to the logic of physiological events involved, type 1 RTA should involve the proximal tubule and type 2 RTA the distal nephron. However, in chronological order, the first form of RTA described was dRTA; therefore, it is called type 1. Type 3 RTA is the combination of reabsorption defects of HCO_3^-, both in the proximal and distal tubules. Type 4 RTA or dRTA with hyperkalemia is caused due to the resistance to the effect of aldosterone or to a deficit of this hormone.

In summary, the current classification takes into consideration three types of RTA: type 2 or pRTA, which reflects the loss of bicarbonate by the kidneys due to reabsorption in the proximal tubule; type 1 RTA or dRTA, also called classical type RTA, which occurs due to failure in the excretion of hydrogen ions in the distal and collecting tubules and, finally, type 4 RTA or dRTA with hyperkalemia, presented by alterations in aldosterone metabolism.[9,10]

ETIOLOGY

pRTA

pRTA is classified as follows:

(A) Primary or isolated—clinically presents with only bicarbonaturia, without other urinary disorders. It may be sporadic or genetic. In turn, those genetically determined are transmitted in an autosomal dominant or recessive manner. The most common hereditary diseases that manifest with pRTA are the following:

a) pRTA with mental retardation and eye disorders
b) deficiency of the enzyme pyruvate carboxylase
c) mitochondrial diseases

(B) Secondary—when pRTA does not occur in isolation but is simultaneously present with other tubular alterations it is called Toni-Debre-Fanconi syndrome and causes different genetic, toxic or immunological alterations such as nephropathic cystinosis, galactosemia, Lowe's syndrome, Dent's disease, tyrosinemia, heavy metal poisoning (lead), Wilson's disease, chronic active hepatitis, accumulation diseases (glucogenosis), Sjögren's syndrome, drug toxicity (such as acetazolamide, gentamicin, cisplatin, lefluonamide, cyclosporine, etc.). Fanconi's syndrome (Toni-Debre-Fanconi) is characterized by the appearance of multiple proximal tubular functional alterations such as glycosuria, tubular proteinuria, aminoaciduria, phosphaturia, calciuria, citraturia, uricosuria, in addition to renal tubular acidosis. Some of the changes mentioned present the risk of progressing to terminal uremia, such as tyrosinemia and cystinosis.[11]

dRTA

(A) Occurs mainly in young children and may be sporadic or hereditary. Some authors include sporadic transient dRTA, but its existence is questionable.[5]

(B) Secondary—vasculitis (Sjögren's syndrome, systemic lupus erythematosus, etc.), Fabry's disease, osteopetrosis, chronic active hepatitis, liver cirrhosis, sickle cell anemia, hyperthyroidism, malnutrition, chronic pyelonephritis, renal transplantation, administration of drugs such as amiloride, amphotericin B, lithium, nonsteroidal antiinflammatory drugs, topiramate, macrolide antibiotics and toxic substances such as toluene.
(C) Hereditary—mutations in two of the subunits of the V-ATPase (ATPase vacuolar or H^+ATPase), carrier protein of hydrogen ions and in the HCO_3^-/Cl^-, AE1 exchanger.

Type 4 RTA

(A) Primary, secondary or genetic hypoaldosteronism
(B) Primary, secondary or genetic pseudohypoaldosteronism
(C) Alterations in aldosterone production such as adrenal insufficiency due to the use of b-blockers, prostaglandin synthesis inhibitors, calcium channel blockers, etc.
(D) Congenital hyporeninemic hypoaldosteronism that most often presents with congenital adrenal hypoplasia due to deficiency of the 18- or 21-hydroxylase, or acquired as in lupus erythematosus, Sjögren's syndrome, mixed cryoglobulinemia, amyloidosis, nephrolithiasis, IgA nephropathy, among others.[12]
(E) Drugs such as inhibitors of angiotensin-converting enzyme (ACE), spironolactone, triamterene, analgesics, NSAIDs, tacrolimus, etc.

PATHOPHYSIOLOGY

Systemic metabolic acidosis is defined as a pathophysiological alteration of the acid-base metabolism caused by acid increase or bicarbonate loss from the extracellular space.[13] The increase in acids (hydrogen ions) occurs in clinical situations that have an excessive production of hydrogen ions and surpasses the capacity of renal excretion, such as what occurs during diabetic ketoacidosis or in prolonged fasting (excessive production of β-hydroxybutyric acid, acetoacetic, etc), in salicylate or propylene glycol poisoning, in lactic acidosis due to cellular hypoxia (infectious, cardiogenic, neurogenic, hypovolemic, etc. or by an effective reduction of renal excretion such as what occurs in chronic or acute kidney injury due to decrease of the glomerular elimination of sulfuric and phosphoric acids. Metabolic acidosis secondary to the reduction of hydrogen ions occurs with a normal concentration of blood chlorine and, therefore, with an elevated blood anion gap.[14]

Moreover, loss of bicarbonate (HCO_3^-) may occur via the intestines or the kidneys. Intestinal loss of bicarbonate occurs during episodes of diarrhea and, less often, with the presence of intestinal fistulas, duodenal-jejunal anastomosis or uretero-sigmoidostomy. When loss of HCO_3^- occurs via the kidneys it is manifested as a systemic hyperchloremic metabolic acidosis with normal serum anion gap and is called RTA in any of its forms: type I, II or IV. Serum anion gap is normal with both the intestinal or renal loss of bicarbonate and both manifest as hyperchloremic metabolic acidosis. Therefore, the differential diagnosis is necessary.

As mentioned, the etiology of metabolic acidosis in acute or chronic renal failure is due to the retention of hydrogen ions by reducing the glomerular filtration rate (GFR), whereas in RTA systemic acidosis is secondary to loss of bicarbonate due to a defect in proximal tubular reabsorption or by a defect in the distal excretion of hydrogen ions which, in turn, results in loss of bicarbonate. The lungs are the organs responsible for the respiratory component, whereas the kidneys contribute to the reabsorption and production of bicarbonate in the large loop of Henle and in the collecting ducts in addition to the elimination of titratable acids and ammonium in the distal tubules to maintain the acid-base balance. In order to achieve excretion of hydrogen ions from metabolism of amino acids and hydroxyapatite formation during growth and bone remodeling in children, excretion of hydrogen ions is coupled to the renal elimination of phosphoric and sulfuric acids (titratable acidity) and, more abundantly, with proximal tubular production of ammonium NH_4^+ (ammoniagenesis) and its excretion in the distal and collecting tubules. Therefore, the net acid excretion (NAE) considers the excretion of hydrogen ions and ammonium in a titratable acid, subtracting the bicarbonate excretion according to the formula:

$$NAE: ([H_2SO_4] + [H_2PO_4^-]) + [NH_4^+] - [HCO_3^-]$$

where NAE: net acid excretion, $[H_2SO_4]$: concentration of sulfuric acid, $[H_2PO_4^-]$: concentration of phosphoric acid, $[NH_4^+]$: concentration of ammonia, $[HCO_3^-]$: concentration of bicarbonate.

The recovery of the filtered bicarbonate binds with the tubular reabsorption of sodium in the proximal tubules, the loop of Henle, the distal tubules and the cortical portion of

the collecting ducts, whereas excretion of hydrogen ions occurs in the medullary portion of the collecting tubules and is independent of sodium metabolism. Tubular reabsorption of sodium requires energy production and oxygen consumption and occurs in connection with the absorption of other substances such as glucose, amino acids, urates, phosphates, sulfates, etc.[15] Tubular transport of sodium is facilitated by the action of transporting proteins on the luminal and basolateral membranes of renal tubular cells as well as by the difference of the electric transmembrane potential.[16] HCO_3^- reabsorption in the proximal tubules as well as most of the solutes is coupled to sodium reabsorption, which occurs via the paracellular and transcellular pathways in about equal amounts.

The pathophysiology of each type of RTA is described beginning with pRTA followed by dRTA and type 4 RTA according to the consecutive order of the normal physiological phenomena of renal tubular reabsorption and with the description of the pathophysiological phenomena involved.

pRTA

The proximal tubules recover the greater part of the bicarbonate filtered by the glomeruli (≅70%) resulting from proton excretion. If one considers that the average GFR in adulthood is 125 ml/min (equal to 180 l/day) and a normal concentration of bicarbonate level in the adult is 24-26 mmol/l, the filtered bicarbonate (GFR x $pHCO_3^-$) is ~4500 mmol/day, which would be lost in the urine if there is proximal tubular failure.

The process of urinary acidification starts at the brush border membrane of the proximal tubule and continues throughout the entire course of the nephron. Although the greater part of filtered HCO_3^- is resorbed in the proximal tubule, the degree of acidification at this site of the nephron is minimal, with a reduction of the pH from 7.40-6.7 or 6.8 which, in relation to the pH of the glomerular filtrate is barely a difference of 0.6-0.7. This indicates that the main task of the proximal tubules is the recovery of filtered bicarbonate. The greatest acidification occurs at the end of the distal tubules, mainly in the collecting tubules due to the excretion of hydrogen ions in the form of titrable hydrogen ions, although in a greater proportion such as ammonia, with the consequent formation of 4-5% of bicarbonate that returns to the extracellular space to exert its buffering action of the acid-base balance at the systemic level.

Therefore, 80% of the filtered bicarbonate is recovered in the proximal tubules and also produces bicarbonate (55 mmol/day) in the process of amoniagenesis, whereas in the collecting tubules bicarbonate is resorbed (4%) during the process of urinary acidification.

It should be mentioned that the threshold of proximal tubular reabsorption of a substance is defined as the maximal plasma concentration at the time during which the substance begins to appear in the urine. Each substance has a specific threshold of reabsorption. In the pediatric age, the threshold of proximal tubular reabsorption of HCO_3^- is dependent on the age and is lower in infants, which is why the bicarbonate plasma concentration is reduced in children under normal conditions.[17] This is a confounding factor in the diagnosis of RTA in children when it is mistakenly believed that the HCO_3^- concentration is equal to that of adults (Table 1). It is also important to take into consideration the altitude, such as that of Mexico City, which is considerable, where the pCO_2 is lower than the pCO_2 at sea level.

Actual knowledge of molecular biology supports the understanding of the proximal tubular physiology and is explained below. The transcellular route of reabsorption, cytoplasmic transport and secretion of different molecules requires transport of proteins that use energy (ATP, ADP) and oxygen consumption in the process. The glomerular filtration that reaches the proximal tubule contains H_2O and electrolytes (Na^+Cl^-, K^+Cl^-, $Na^+HCO_3^-$, Ca^{2+}, $H_2PO_4^-$, SO_4^{2-}) as well as glucose, urates, citrate and some amino acids.[14] Transcellular transport reabsorption of Na^+ is carried out through the apical and basolateral membranes of the proximal tubule. Also, oxalate, organic anions, ammonia, toxins and Na^+ are excreted towards the tubular lumen. In turn, reabsorption of 70-80% of HCO_3^- in the

Table 1. Normal blood gas values according to age[13,50]

Age	*pH*	*PaO_2 (mmHg)*	*$PaCO_2$ (mmHg)*	*HCO_3^- (mEq/l)*
Newborn				
Premature	7.20-7.25	50-60	50-55	16-18
Term 1 day	7.26-7.27	60	55	13-22
<28 days	7.37	70	33	20
Lactant				
1-24 months	7.40	90	34	20
2-18 years	7.39	96	37	22-24
Adult	7.35-7.45	90-110	35-45	24-26

proximal tubule unites with the secretion of H^+ in the lumen by the concerted action of the Na^+/H^+ (NHE3) exchanger and the ATPase of H^+ (or V-ATPase, vacuolar) in the apical membrane. Sodium bicarbonate molecules are not resorbed as such but are split in the tubular lumen into Na^+ and HCO_3^- molecules and later in CO_2 and H_2O by the catalyzing action of the carbonic anhydrase enzyme IV, present in the luminal or apical membrane of the cells of the brush margin (Figure 1). Approximately 60% of the CO_2 diffuses towards the cytoplasm of the proximal tubules through gas and water channels (aquaporines AQP1).[18] Once in the cytoplasm, carbonic anhydrase II catalyzes the hydration of CO_2, the biochemical reaction is reversed and the HCO_3^- molecule is once again formed. Transcellular transport of $NaHCO_3$ ends in the basolateral membrane due to the concerted action of the sodium-potassium pump (Na^+K^+ATPase) and the co-transporter of the Na^+/HCO_3^- (NBCe1). The mechanisms of transport maintain the electromotive strength required for the reabsorption of the other solutes in the proximal tubule. NBCe1 was identified for the first time in the salamander tubules.[19] The *SLC4A4* gene that codifies the NBCe1 transporter was also isolated in these tubules.[20]

Five variants of the NBCe1 (A-E) transporter have been identified. The NBCe1-A transporter is amply expressed in the kidney.[21] The NBCe1-A transporter comprises 14 transmembrane segments. The N-terminal region has eight segments homologous to the Cl^-/HCO_3^-(AE1) exchanger; in contrast, the C-terminal region has six transmembrane segments that differ from the AE1 exchanger.[22] The NBCe1-B transporter is distributed in various tissues and is more abundant in the pancreas.[23] The NBCe1 transporter as well as the AE1 exchanger facilitate the bicarbonate transport towards the blood flow through the basolateral membrane of the renal tubular cell (Figure 1).

Mutations of the *SLC4A4* gene are associated with the autosomal recessive pRTA. Patients may present with ocular and dental abnormalities, low stature and mental retardation. Pathophysiology of pRTA is explained by the role of the NBCe1-A transporter in the proximal tubular epithelium. NBCe1-A mutations cause the elimination or decrease in its activity. Until now, 12 mutations have been identified in the *SLC4A4* gene in patients with pRTA.[24-30] With the exception of the p.Asn29X mutation, which only affects the variant NBCe1-A, all mutations of the pRTA alter the five variants of the NBCe1 transporter. It is unknown to what degree extrarenal symptoms are due to defects in the expression of the NBCe1-B-E transporters or to the secondary effects of systemic acidosis as a result of the lack of activity of the NBCe1-A transporter. It is important to underline that the V-ATPase (H^+ATPase) of the proximal tubule expresses the B2 subunit, unlike the V-ATPase of the collecting tubules and of the internal ear epithelium that only express the B1 subunit.[31]

In theory, changes of each of the mechanisms that participate in the reabsorption of sodium bicarbonate (NHE3, AC II, AC IV, NBCe1, AE1 and the Na^+K^+ ATPase), both hereditary as well as acquired, could cause a reduction in the reabsorption of HCO_3^- and result in the development of pRTA. However, until now, only two target molecules have been detected whose mutations produce pRTA. These are the Na^+/HCO_3^- (NBCe1) co-transporter and the intracellular AC II. The latter creates a combined proximal and distal RTA because the AC II is functionally located in both the proximal tubule and in the end part of the distal tubule.[32] Some authors believe this is a combination of defects of ion transport such as type 3 or mixed RTA.[32]

pRTA is therefore characterized by a reduction in the proximal tubular capacity of bicarbonate reabsorption with an important increase of its distal contribution and urinary loss with the elevation of urinary pH because the distal tubules have a limited physiological capacity for bicarbonate reabsorption . Generally, the cause is due to a hereditary or acquired defect that prevents maintaining a normal concentration of plasma bicarbonate in the presence of a normal production of dietary acids and from normal organic metabolism.

As systemic metabolic acidosis increases, plasma bicarbonate filtered by the glomeruli decreases proportionally so that the capacity for reabsorption of filtered bicarbonate increases in a relative manner. This process continues until the plasma HCO_3^- reduces below threshold and the proximal tubular reabsorption is increased to its maximal capacity, which decreases the distal bicarbonate load. Because the distal tubular function is intact, urinary pH is reduced <5.5. For this reason, children with pRTA with serious systemic acidosis, or during acute clinical periods, are able to acidify the urine. However, the urine becomes alkaline after bicarbonate administration.

Hypocitraturia is not present in pRTA so it is not generally accompanied by renal lithiasis and nephrocalcinosis.[33] In addition, distal calcium is found to be increased,

its distal tubular reabsorption is also increased and the risk of nephrocalcinosis is decreased.

Apart from the presence of systemic metabolic acidosis, pRTA presents clinically with frequent vomiting, episodes of diarrhea, growth retardation and hypokalemia. Vomiting and growth retardation are explained by persistent metabolic acidosis, lack of appetite and polydipsia and polyuria secondary to the loss of urinary sodium and bicarbonate. Loss of sodium implies contraction of the volume of the extracellular space and, as a response, the secretion of renin and aldosterone increases. Loss of urinary potassium is facilitated and there is a reduction of its plasma concentration. In the isolated form of pRTA, calcium and vitamin D metabolism remain normal, but alterations take place with Fanconi's syndrome with an important arrest in growth and, consequently, rickets.

dRTA

Final regulation of the acid-base metabolism is carried out in the distal and collecting tubules. In this section of the nephron, reabsorption of filtered bicarbonate is only 5-10% as opposed to the proximal tubule where the greater portion is resorbed (70-80%) and the ascending branch of the loop of Henle (20-30%). This occurs because of the hormonal regulation (angiotensin II and aldosterone) of the proton secretion, with reduction of the urinary pH up to 4.0-4.5 under extreme conditions of acute systemic acidosis. In turn, in the presence of systemic alkalosis, bicarbonate is secreted in the collecting tubules by the β-intercalated cells, resulting in a urinary pH of up to 8.0-8.5. Therefore, in the end part of the nephron, mainly in the collecting tubules, correction and compensation of the systemic alterations of the acid-base metabolism occur.[8]

In the collecting tubules, acidification depends on sodium transport in the principal cells and is subjected to transepithelial voltage. Active reabsorption of sodium generates a difference of the negative electrical potential that facilitates secretion of hydrogen ions. This mechanism is increased by the action of aldosterone that increases even more the negative transepithelial difference of the voltage with an increase in the acidification (Figure 2). Urinary acidification in the medullary collecting tubule occurs due to the electrical gradient that facilitates the secretion of hydrogen and potassium ions. Secretion of protons in the medullary portion of the collecting tubules is greater than in the cortical portion. Secretion of hydrogen ions in the medullary portion of the collecting tubules occurs because of the action of two transporting proteins, also called hydrogen ion pumps, located in the α-intercalated cells. H^+ATPase (V-ATPase) regulated by aldosterone and H^+K^+ ATPase also respond in an inverse manner to the plasma concentration of K^+. The H^+ molecules that are secreted towards the lumen bind to different buffer systems, mainly phosphates (titratable acidity) and ammonia (NH_4^+), to finally be excreted in the urine.[34] Final reabsorption of cellular $NaHCO_3^-$ towards blood flow is carried out by the Cl^-/HCO_3^- (AE1) interchanger located in the basolateral membrane. H^+K^+ ATPase expresses 13 subunits and numerous isoforms and responds to the extracellular potassium concentration, regulating its metabolism. Also, hydrogen ions are secreted in exchange for potassium ions in the apical membrane of the α-intercalated cells (Figure 3).[34]

The physiological mechanism of the organism for hydrogen ion elimination is the kidney, and its most efficient form of secretion lies in the formation of an ammonia/ammonium buffer solution (NH_3/NH_4^+). NH_3 is produced in the proximal tubular cells from glutamine metabolism and is excreted into the tubular lumen in the form of NH_4^+, which is recycled in the loop of Henle and is eliminated in the urine in the collecting tubules (Figure 4). Any alteration of the physiological mechanisms of urinary acidification in the distal and collecting tubules can give rise to dRTA which, in the majority of cases, is believed to be a hereditary disease in which the hydrogen ions cannot be eliminated.[35]

This disorder is characterized also by polyuria, loss of urinary potassium with reduction of its blood concentrations, as well as calcium loss in the urine, which favors growth delay and the appearance of rickets. Also, hypocitraturia is present, which frequently triggers the production of stones and nephrocalcinosis, complications that could potentially present a risk of progression to ESRD.[36]

The following is a presentation of recent information on the molecular biology of transporters and channels of α-intercalated cells, which are secretors of acid localized in the collecting tubule and are considered relevant for a better understanding of RTA.

Secretion of hydrogen ions (H^+) in the urine is carried out in α-intercalated cells of cortical and medullary collecting ducts. V-ATPase (H^+ ATPase) catalyzes the pas-

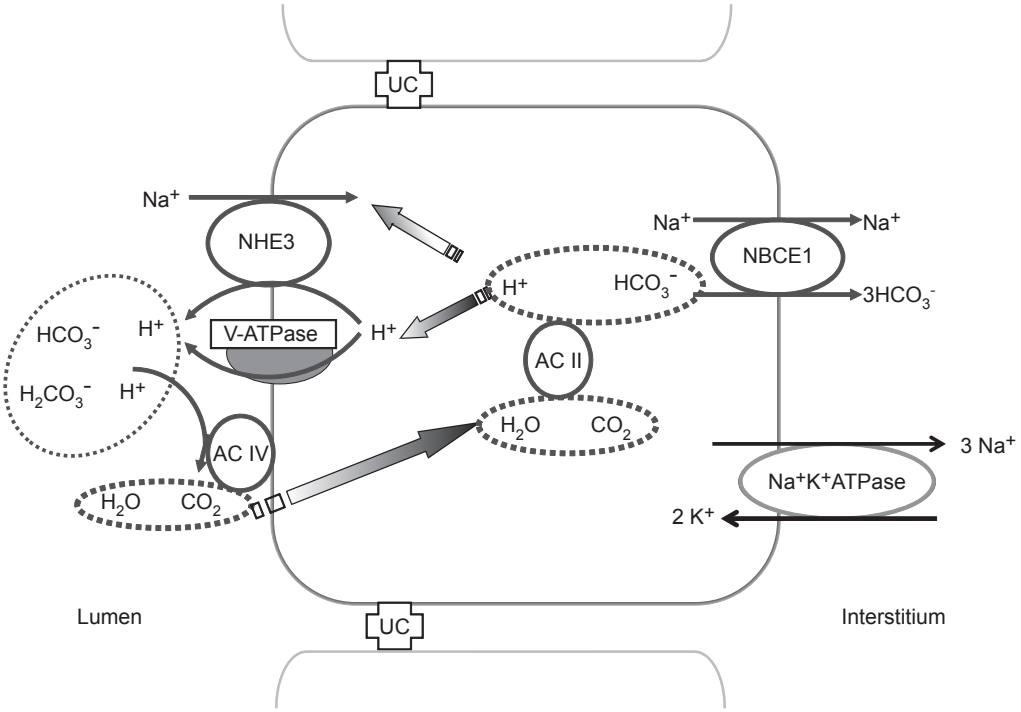

Figure 1.

Proximal tubule. Scheme of the reabsorption of sodium bicarbonate ($Na^+HCO_3^-$) in the proximal tubule. Bicarbonate filtered at the glomerulus is combined with hydrogen ions (H^+) secreted by the Na^+/H^+ (NHE3) exchanger and V-ATPase. Carbonic anhydrase AC IV, present at the apical membrane, catalyzes the formation of carbon dioxide (CO_2). CO_2 diffuses into the cytoplasm passively through channels (not shown). AC II carbonic anhydrase generates HCO_3^- and H^+. HCO_3^- is transported to the interstitial space by the NBCe1 cotransporter present in the basolateral membrane.

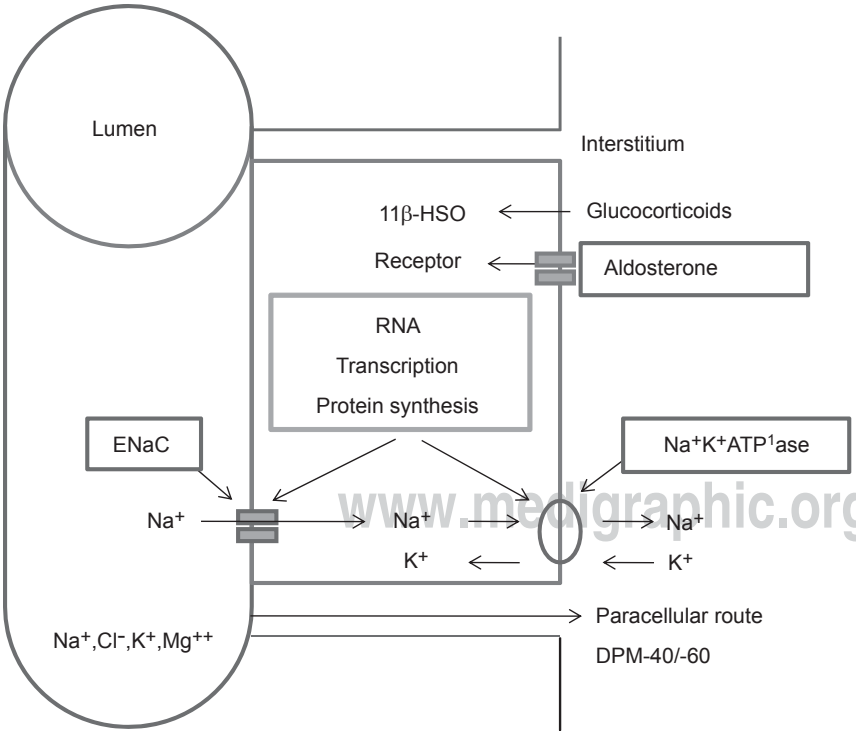

Figure 2.

Principal cell. Aldosterone exerts its action on the principal cell of the distal tubules after it binds to its receptor and stimulates the synthesis of the sodium/potassium pump (Na^+K^+ATPase) and sodium channels (ENaC). These physiological actions facilitate the reabsorption of sodium and potassium and proton excretion in the distal nephron.

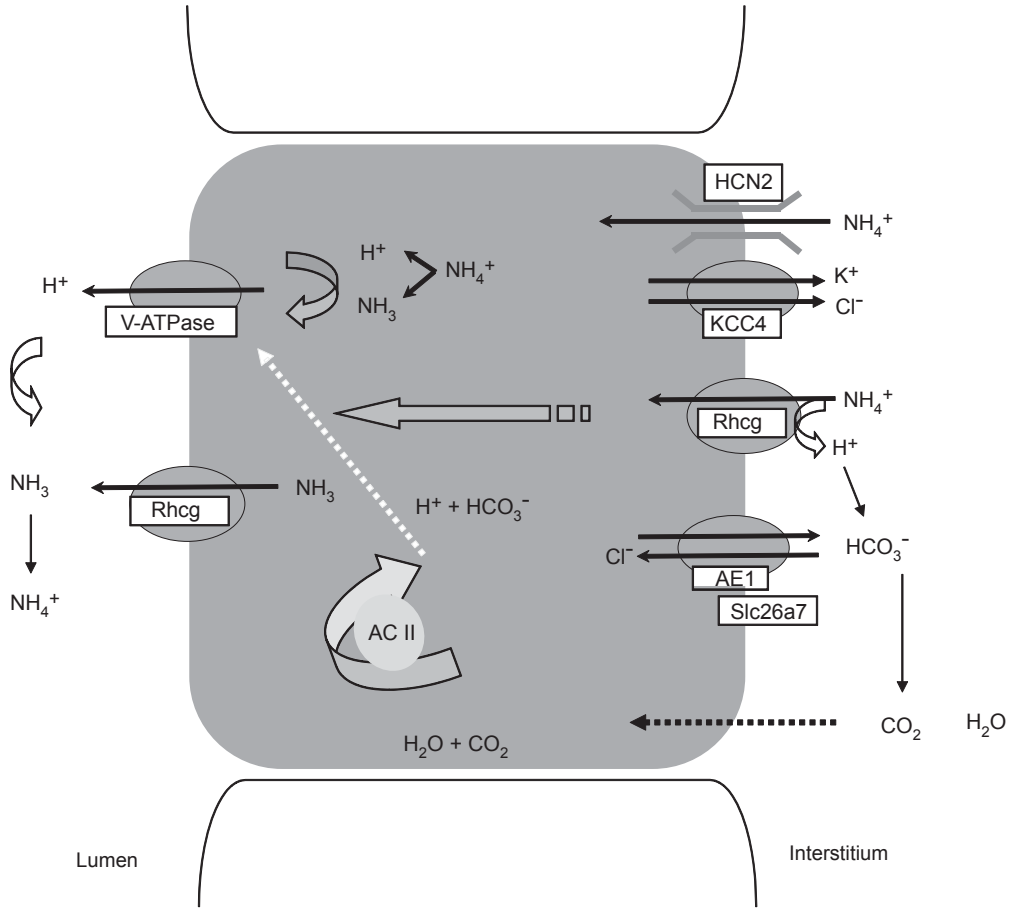

Figure 3.

Collecting tubule of the α-intercalated cell. Model of the excretion of acid load in urine and reabsorption of Na^+ HCO_3^- in an intercalated acid secretory cell. Transcellular transport of ammonium (NH_4^+) is carried out from the interstitial space towards the lumen via three pathways. The ammonia can be taken up by the KCC4 transporter, Rhcg ammonia channel and HCN2 ammonium channel. HCO_3^- is resorbed through the AE1 exchanger. Aldosterone stimulates the production of H^+ ATPase (metabolic effect independent of Na^+), which transports H^+ into the lumen and produces titratable acids, whereas the Rhcg ammonia channels transport and excrete ammonia in the urine.

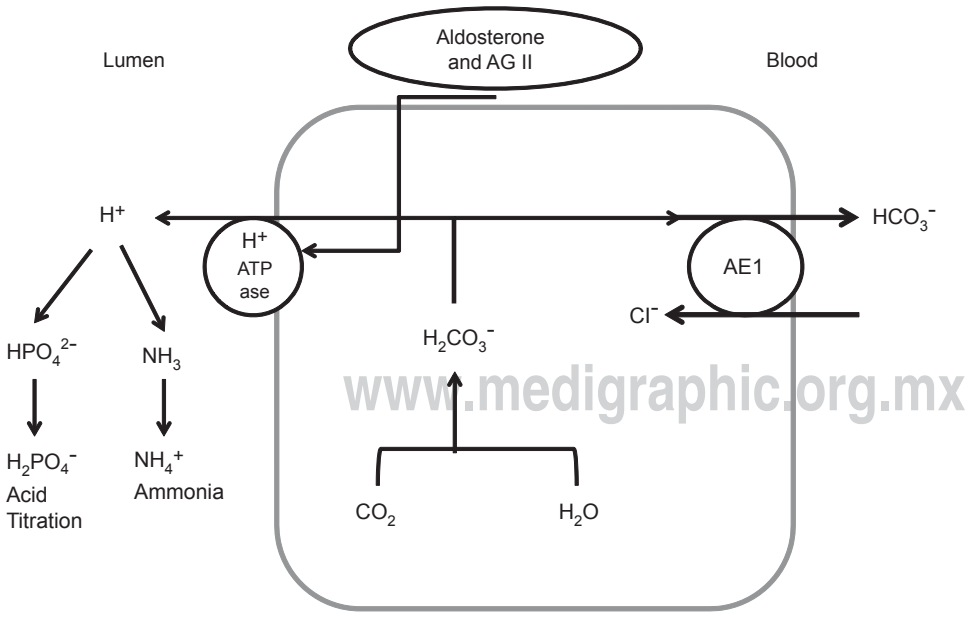

Figure 4.

Secretion of hydrogen ions in α-intercalated cell. The action of aldosterone on H^+ ATPase is shown. In turn, H^+K^+ ATPase is regulated by the $[K^+]$ in the extracellular space. The protons secreted to the tubular lumen join phosphates and sulfates to form titratable acids and ammonia to be removed in the urine in the form of ammonium (NH_4^+).

sage of H^+ from the cytoplasm to the lumen. Carbonic anhydrase ACII catalyzes the production of H^+ and HCO_3^-; the latter is absorbed through the Cl^-/HCO_3^- AE1 exchanger in the basolateral membrane (Figure 2).

The *SLC4A1* gene encodes the AE1 exchanger, a dimeric glycoprotein with 12 to 14 transmembranous domains.[37,38] AE1 participates in pH regulation, cell volume and intracellular transport of acid and base in epithelial cells.[39,40] AE1 has a specific isoform of erythrocytes and a short isoform specific to the kidney. In the erythrocytes, AE1 has a structural role because it interacts with cytoskeletal proteins. In the kidney, AE1 carries out reabsorption of HCO_3^- towards the interstitial space and blood vessels.[41,42]

A group of mutations in AE1 cause erythrocyte deformations. Their origin is of the autosomal dominant hereditary type: hereditary spherocytic anemia, the South-Asian ovalocytosis and other stomacytoses with normal renal function.[43] However, there is another series of mutations in AE1 that generate dRTA, either alone or accompanied by alterations in the erythrocytes.[4]

V-ATPase is a complex multimeric enzyme consisting of 14 subunits and with two domains: one in the cytoplasm (V_1) and another in the membrane (V_0). V_1 is the catalytic domain and consists of eight subunits (A-H). The V_0 domain encompasses six subunits (a, c, c", d, e, and Ac45) and translocates the H^+ through the membrane.[44] The catalytic sites are in the A1 subunit and the interface between subunits A-B regulate the activity of the enzyme. The subunit "a" in V_0 allows access to hemichannels through which the hydrogen ions H^+ are exported into the luminal space.[45]

In the α-intercalated cells of the distal tubules, V-ATPase is located in the apical membranes and secretes acid in the urine (Figure 3). B1 subunits and a4 of the V-ATPase are specific to the a-intercalated cells. Defects in any of these two subunits give rise to dRTA.[46] Because the B1 subunit is also is expressed in ciliary cells of the internal ear,[3] mutations in the B1 subunit produce dRTA with deafness. There are other transport systems in the a-intercalated cells of the distal nephron that also participate in the acid-base homeostasis such as carbonic anhydrase II,[44] co-transporters of K-Cl KCC4,[47] ammonia channels of Rhcg,[48,49] and the ammonia channel HCN2 (Figure 3).[50,51] H-K-ATPase does not appear to participate in the acid secretion, but in the reabsorption of K^+ under conditions of hypokalemia.[40]

The mechanism of ammonia NH_4^+ excretion is carried out in two stages. First, it is transported from the interstitial space of the cytoplasm of the intercalated cells by ammonia channels activated by HCN_2 voltage or by Rhcg ammonium channels. HCN2 channels are constitutive and are only located in the basolateral membranes; they can capture either ammonia or sodium and are not regulated by metabolic acidosis. In contrast, the channels of Rhcg ammonium are located in the cytoplasm and its transport to the apical membranes as well as to the basolateral membranes is regulated by metabolic acidosis.[47,48] It is important to underline that transcription, translation, and transport to the membrane of the majority of the transporters described are dependent on systemic metabolic conditions.

Microperfusion trials of the tubules and models of elimination of some of the transporters in mice (*knockout*) have helped to elucidate the routes of transport that participate in the acid-base homeostasis in the α-intercalated cells. Mice that do not express KCC4 develop neurosensorial deafness as well as dRTA.[49] There is another interchanger of Cl/bicarbonate that also operates as a channel of Cl^-, the Slc26a7. The mouse $Slc26a7^{-/-}$ presents complete dRTA. Mice without the ammonium channel $Rhcg^{-/-}$ have problems with ammonia excretion only under conditions of metabolic acidosis, such as in the case of an incomplete dRTA.[50] The ammonia HCN2 channel is a constitutive ion channel that participates in the basal excretion of ammonia, but does not appear to be regulated by metabolic acidosis.[51,52]

TYPE 4 RTA

Type 4 RTA is associated with alterations of the aldosterone and renin-angiotensin system. Renin is produced in the juxtaglomerular apparatus and in the liver is converted to angiotensin I (Ang I) by the action of angiotensinogen. In the lungs, Ang I is converted to angiotensin II (Ang II) by action of the convertase enzyme.[5] Ang II exerts its vasoconstrictive power in the systemic arterial system and stimulates the production of aldosterone whose function is the distal tubular reabsorption of sodium and the interchange by hydrogen ions or potassium ions. Therefore, it contributes to the expansion of the extracellular space and to elevate systemic arterial pressure. Unlike other types of RTA, type 4 is characterized by the tendency towards hyperkalemia. The most common form of RTA, both in children as well as in adults,[53] is perhaps due to its associ-

ation with numerous clinical disorders, mainly obstructive uropathy, common at all ages. However, in children the most frequent etiology of type 4 RTA is genetic. The main pathophysiological alteration in this disease is related to deficiency in the production and secretion of aldosterone (hypoaldosteronism) or renal tubular resistance to its action (pseudohypoaldosteronism).[10,52]

Aldosterone is produced in the glomerulous zone of the adrenal cortex from its precursors (cholesterol, pregnenolone and deoxycorticosterone, 18-OH corticosterone). It is stimulated by the action of the renin-angiotensin system (Ang II and III) and the concentration of K^+ ion in the extracellular space. Aldosterone acts on the principal cells of the distal tubules, facilitating reabsorption of sodium in exchange for potassium ions excreted in the urine as well as in a-intercalated cells of the collecting tubules, stimulating the secretion of hydrogen ions. Aldosterone production stimulates the sodium-potassium pump (Na^+K^+ ATPase) and the expression of the epithelial sodium channels (ENaC) in the principal cells of the distal tubules (Figure 4). As mentioned, aldosterone facilitates Na^+ reabsorption in the principal cells and the excretion of H^+ in the α-intercalated cells, which increases the electronegativity of the tubular lumen and K^+ excretion in the principal cells. In turn, it stimulates the production of ammonia in loading of the proximal and distal tubules. In the presence of hypoaldosteronism or pseudohypoaldosteronism, the formation of NH_4^+ and HCO_3^- reabsorption is reduced with development of metabolic acidosis. Also, excretion of K^+ is reduced, which explains the hyperkalemia.[53]

Patients with type 4 RTA have a reduction in the net acid excretion secondary to a decrease in the production and distal tubular excretion of NH_4^+. Bicarbonate reabsorption is also found to be reduced and bicarbonaturia is produced. However, when metabolic acidosis worsens, whether due to diarrhea or stress, plasma bicarbonate is reduced below its threshold of reabsorption and the urine is acidified with reduction of the urinary pH ≤ 5.5, similar to what occurs in pRTA. The differential diagnosis is deduced by the presence of hyperkalemia in case of type 4 RTA whose etiology is hypoaldosteronism or pseudohypoaldosteronism.[54,55]

DIAGNOSIS

Suspicion of RTA is based on the clinical presentation and is corroborated with laboratory data in the presence of systemic hyperchloremic metabolic acidosis. To determine the type of RTA it is necessary to measure the urinary anion gap of the ammonia excretion as well as the difference in the partial pressure of carbon dioxide (pCO_2) in blood and urine. In some cases of difficulty in diagnosis, the systemic acidification test with titration of urinary bicarbonate can be used. However, this test is in disuse due to risks to the patient.

(A) Clinical manifestations

a) In primary or isolated RTA there is anorexia, thirst, polyuria, growth arrest, episodes of vomiting and diarrhea with tendency towards dehydration and rickets (Table 2). Nephrolithiasis and nephrocalcinosis are generally absent in pRTA and are more frequently found in dRTA and type 4 RTA.
b) In pRTA secondary to systemic diseases, symptoms of systemic disease tend to predominate and generally are accompanied by multiple defects in proximal tubular reabsorption.

(B) Laboratory findings[56,57]

a) Urinary pH. Urinary pH interpreted in an isolated manner is not useful in the diagnosis of RTA. However, it is of unquestionable support when interpreted in the context of the rest of the labo-

Table 2. Diagnosis of primary RTA

1. Clinical presentation: growth delay, polyuria, thirst, anorexia, rickets, lithiasis, nephrocalcinosis
2. Hyperchloremic metabolic acidosis in absence of extrarenal loss of bicarbonate (due to diarrhea or intestinal fistulas)
3. Blood pH (pHs) is generally found to be normal due to the presence of compensatory respiratory alkalosis. Periods of exacerbation of metabolic acidosis can be reduced due to acute diarrhea or physical stress. Concentration of bicarbonate generally is reduced.
4. Urinary pH (pHu) persists >6.5, except in pRTA and in type 4 RTA, during acute episodes of metabolic acidosis due to physical stress or diarrhea when the concentration of bicarbonate is less than the threshold of proximal tubular reabsorption of bicarbonate
5. Blood anion gap or R(residual) fraction, also called indeterminate anion fraction:
   - HAs: $[Na^+] - ([Cl^-] + [HCO_3^-]) = 10 + 5$
   - HAs <15 RTA (in the absence of intestinal loss of HCO_3^-)
   - HAs >15 Metabolic acidosis due to retention of hydrogen ions (lactic acidosis, ketoacidosis, retention of sulfuric and phosphoric acid in renal insufficiency intoxication due to salicylates)

ratory tests. In the presence of RTA, urinary pH is generally >5.5 (average 6.5-7.5). However, it may be less in pRTA and in type 4 RTA when the systemic acidosis becomes acute and the plasma bicarbonate is reduced below the threshold of tubular reabsorption, which can occur during stressful situations and episodes of diarrhea. In both types of RTA, distal acidification is found to be intact. Therefore, when the distal contribution of bicarbonate is reduced, distal reabsorption is complete, with the possibility of acidification of the urine and reduction of the urinary pH <5.5. In turn, in dRTA, urinary acidification is incomplete or is absent, so that the urinary pH is not reduced <6.0. Administration of bicarbonate increases its urinary excretion, with increase of the urinary pH in all types of RTA.

b) Systemic acidosis. In RTA there is hyperchloremic metabolic acidosis with normal blood anion gap, which is determined according to the following formula:

$$[Na^+] - ([Cl^-] + [HCO_3^-]) = 12 \pm 4 \text{ mmol/l}$$

This is useful in older children and adults, whereas the normal figures for children <2 years is 16 ± 4 mmol/l (Table 2). When the result is greater than this number, it is considered that metabolic acidosis is secondary to hydrogen ion retention. In turn, when the urinary anion gap is normal, metabolic acidosis is secondary to the loss of bicarbonate and is as a result of intestinal losses (diarrhea, fistula) or via the kidney. Diagnosis is compatible with the presence of RTA.

c) Determination of arterial gases demonstrates a reduction of the pH, total CO_2 and bicarbonate concentrations during the periods of severe acidosis. However, in stable conditions, blood pH is normal (7.40 ± 0.05) due to the regulatory mechanism of pulmonary compensation. The $[HCO_3^-]$ remains reduced, indicating that we are dealing with a hyperchloremic metabolic acidosis with compensatory metabolic alkalosis. It is important to mention that the blood sample used for determination of blood gases should preferentially be from arterialized blood. However, due to the technical difficulty, especially in newborns and infants, the sample can be substituted with arterial venous blood without applying a tourniquet. This is achieved by applying mild heat to the extremity (warm water or thermal irradiation) with the objective of increasing blood flow and equalizing the pCO_2 from the venous side to the arterial side in the capillary bed. Careful attention should be given to avoiding skin burns. Blood sample using nonarterialized venous blood lacks usefulness in the diagnosis of RTA.

d) Hypokalemia. The concentration of K^+ is found to be reduced in pRTA and dRTA due to the increase of urinary flow with an important loss of ions. Also contributing are the gastrointestinal losses. Increase in the $[Cl^-]$ is fortuitous, dependent on $[HCO_3^-]$ reduction and has no physiological implication in the development of metabolic alterations.

e) Hypocitraturia and hypercalciuria are part of dRTA. The normal figure of citrate excretion is >180 mg/g of creatinine and calcium excretion is <4 mg/kg/day.

f) Excreted fraction of filtered bicarbonate (EFBi). EFBi allows for differentiation of pRTA from dRTA and, for its determination, administration of sodium bicarbonate is required until a minimum concentration in blood of 22 mmo/l is achieved. EFBi is increased 10-15% in pRTA and is <5% in healthy children and in dRTA (Table 3). EFBi is calculated with the formula:

$$[HCO_3^- u]/ [HCO_3^- s] /[Cru]/[Crs] \times 100$$

where $[HCO_3^- u]$: concentration of urinary bicarbonate, $[HCO_3^- s]$: concentration of blood bicarbonate, [Cru]: concentration of urine creatinine, [Crs]: concentration of blood creatinine.

g) Determination of the gradient of the pCO_2u-pCOs helps to distinguish pRTA from dRTA and, at present, is considered the most sensitive diagnostic method to detecting alterations in the secretion of hydrogen ions in the collecting duct. In dRTA, the urine/plasma gradient of pCO_2 (pCO_2u-pCO_2s) is <20 mmHg, independent of whether the dRTA is primary, secondary or hereditary, whereas in pATR and in healthy children it is >20 mmHg.[58,59]

h) Determination of the urinary anion gap is used with the objective of diagnosing RTA *vs* the presence of metabolic acidosis of any other etiology (Table 3). It consists of measuring the concentration of electrolytes in the urine and applying the following formula:

$$[Cl^-] - ([Na^+] + [K^+]$$

In this case, the indeterminate ion is the ammonium (NH_4^-). It is interpreted that the excretion of protons and ammonium is normal when the result is $\leq$50 mmol/l and diagnosis of RTA when the figure is $\geq$50 mmol/l. With these figures, other causes of metabolic acidosis are ruled out. Determination of the urinary anion gap is used with less frequency at present because the results are not always reliable.

i) Acidification tests with ammonium chloride or furosemide stimulation. Acidification tests were the gold standard for diagnosis of dRTA for a period of time.[60] At present, they are only used when there is an asymptomatic defect in the acidification of the urine without systemic acidosis (a condition known as incomplete dRTA acidosis). It has been proposed as a diagnostic measure that would allow for timely treatment to be initiated as well as for detecting a partial alteration of the regulatory mechanisms of the acid-base balance (Table 4).[61]

The original diagnostic technique is as follows:

- Admission of the patient without previous preparation and with a normal diet
- Urine sample is obtained at 3 h to determine pH, titratable acidity and ammonia
- Ammonium chloride syrup is given at 8 a.m. (75 mEq/m^2 SC or 4 g/m^2 SC), considering that one gradient of ammonium chloride contains 19.2 mEq of ammonia and chloride.
- Samples of blood and urine are taken at 11 a.m., 2:00 p.m. and 5:00 p.m. for pH, titratable acidity and ammonium.

However, this technique has fallen into disuse because it lasts 8 h and patients often present nausea, vomiting and gastric irritation.

A variation of this test is oral furosemide administration in order to increase the sodium load in the distal nephron, previously carrying plasma bicarbonate to normal levels. The changes in urinary pH are more pronounced in patients with sodium depletion or with the administration of a mineralocorticoid. A test has also been proposed that considers the use of furosemide at 1-2 mg/kg, adding fludrocortisone as a simple and safe diagnostic alternative.[62]

It should be noted that it is important to carry out a renal ultrasound to detect hydronephrosis and congenital malformations as well as nephrocalcinosis. The latter can

Table 3. Differential diagnosis of RTA

1. Urinary anion gap. In the urinary anion gap, the indeterminate anion is ammonia (NH4+). Most hydrogen ions are attached to NH4- NH4+ to be excreted in the urine. Urinary anion gap is useful for detecting a reduction in ammonia excretion due to a defect in the distal tubular proton secretion and is calculated as follows:

   Anion gap: [Cl-] – ([Na+] + [K+]): normal = –50

2. Positive anion gap result is positive when >–50, indicating the presence of RTA. With a positive result, along with a reduced urinary excretion pCO_2, causes of metabolic acidosis other than RTA can be ruled out
3. Excreted fraction of filtrated bicarbonate (EFBi)

   Utilized always to classify type of RTA and when there is a diagnosis of systemic metabolic acidosis with hyperchloremia (reduced concentration of plasma bicarbonate) and HAs = 15 + 5

   EFBi: 100 x (U/P) HCO_3^-/(U/P) Cr

   EFBi >15%: pRTA

   EFBi <5%: normal individuals and dRTA
4. Urinary excretion of pCO_2. Method is highly utilized for diagnosis of dRTA of any etiology, once the presence of hyperchloremic metabolic acidosis has been determined
5. pCO_2 u–pCO_2 s

   Normal individuals and pRTA: >20 mmHg

   dRTA: <20 mmHg

Table 4. Normal elimination of hydrogen in a state of maximum serum acidification according to age

	Term newborns	*1-12 months*	*2-16 years*
Urinary pH	≤5.0	≤5.0	≤5.0
Ammonium (µEq/min/1.73 m^2)	55.8 (56-68)	57 (42-79)	73 (46-100)
Titratable acids (µEq/min/1.73 m^2)	32.4 (25-50)	62 (43-11)	52 (33-71)

also be detected with plain abdominal x-ray, computed tomography (CT) or lumbar magnetic resonance. Ultrasound is more sensitive than plain x-ray and CT is more specific than ultrasound, but implies greater exposure to radiation. It is classified according to the affected area as medullary, cortical or diffuse.[63]

TREATMENT

Treatment depends on the type of acidosis and the etiology. The objective of treatment is to correct the acidosis and other electrolyte and biochemical abnormalities that may accompany the acidosis such as hypokalemia, hypocitraturia, hypercalciuria, hypophosphatemia in order to achieve better growth and prevent development of nephrocalcinosis.[64] In the presence of severe hypokalemia, one must first correct the potassium deficiency and then correct the acidosis.

Alkalinizing treatment is achieved with the administration of citrates or bicarbonates such that the production of endogenous hydrogen ions is compensated and the blood bicarbonate is increased to normal levels for age (Table 5).[64]

Patients with dRTA generally require an alkaline dose of 1-3 mEq/kg/day, requiring dose adjustments until the hypercalciuria and hypocitraturia are normalized. Patients with pRTA require larger doses, usually between 10 and 15 mEq/kg/day. The total dose is divided in order to be administered three or four times daily, and a higher nighttime dose is recommended.

In addition to the alkalinizing treatment, patients with Fanconi's syndrome secondary to cystinosis should receive phosphocysteamine, phosphates and vitamin D.[11] Similarly, children with rickets and hypophosphatemia should receive supplemental calcium, vitamin D and phosphates.[65]

Citrate is useful in the presence of hypocitraturia in conjunction with hypercalciuria as in some cases of dRTA. Potassium citrate is preferred instead of sodium citrate because the latter favors hypercalciuria. Citrate is converted to bicarbonate in the liver on entering the Krebs cycle. Alkalinization of the urine reduces reabsorption of citrate and increases solubility of cystine, calcium oxalate and uric acid, with a tendency to reduce the development of nephrolithiasis and nephrocalcinosis. However, care must be taken not to over-alkalinize urinary pH because it may favor the precipitation of calcium phosphate.[66]

In cases of type 4 RTA (hyperkalemia), use of alkalinizing solutions without potassium are recommended. Treatment with mineralocorticoids may be required.[67] In some cases with difficult to control hyperkalemia, the use of diuret-

Table 5. Alkalyzing treatment

Name	*Formula*	*Alkaline and electrolyte support*
Citrates		
Citrate solution[8]	Sodium citrate 98 g Potassium citrate 108 g Citric acid 70 g Addition of 200 ml of syrup* diluted to 1000 ml with bidistilled water Commercial names: Polycitra, Tricitrates, Cytra 3	1 ml = 1 mEq Na, 1 mEq K, 2 mEq HCO_3
Potassium citrate solution	Commercial name in solution: Uroclasio NF Commercial name: Polycitra K, Cytra K	5 ml = 14 mEq K, 14 mEq HCO_3
Powder crystals	Commercial name: Polycitra K crystals, Cytra K crystals	1 packet = 30 mEq K, 30 mEq Na
Citrate solution without potassium[8] (Shohl's solution)	Sodium citrate 90 g Citric acid 140 g Add 200 ml of syrup* and dilute to 1000 ml with bidistilled water	1 ml = 1 mEq HCO_3, 1 mEq Na
Bicarbonate		
Bicarbonate solution[8]	Sodium bicarbonate 43 g Potassium bicarbonate 53 g Dilute to 500 ml with bidistilled water and syrup*	1 ml = 1 mEq Na, 1 mEq K, 2 mEq HCO_3
Sodium bicarbonate	Powdered crystals	1 g = 12 mEq HCO_3
Potassium bicarbonate	Powdered crystals	1 g = 10 mEq HCO_3

*Syrup flavor depends on patient preference. Those most utilized are currant, grape, lime and mandarin. Some patients prefer the solution without the addition of syrup.

ics or cationic exchange resins such as Resincalcio® that exchange calcium for potassium in the intestinal lumen, as well as Kayexalate® that exchanges sodium for potassium also in the intestine, may be required.[62] The use of formulations that combine sodium citrate with potassium citrate at lower doses of each of its components is frequent such as citrate solutions Trycitrate® or Polycitra® because potassium citrate at high doses may be an irritant to the digestive tract mucosa. Also, citrate such as Shohl's solution can be administered, which does not contain potassium, or crystal citrate (Table 5). Administration of an alkalinizing agent is recommended after the ingestion of foods. Taken with water or other liquids such as milk or juice, it is better tolerated. The most common adverse treatment effects are gastrointestinal including bloating, stomach upset, nausea, vomiting, and diarrhea. Rapid correction of the hyperchloremic metabolic acidosis can lead to the development of hypocalcemia or hypokalemia, mainly when potassium salts are not administered concomitantly.

For obvious reasons, potassium salts should not be prescribed in the presence of adrenal insufficiency (Addison's disease), pre-existing hyperkalemia, anuria or in patients with heart failure receiving digitalis because it increases the risk of toxicity as well as the use of other drugs that increase plasma potassium such as potassium-sparing diuretics (spironolactone, eplerenone and amiloride), ACE inhibitors such as captopril and lisinopril, and angiotensin receptor blockers (losartan).

In some cases hypercalciuria and hypocitraturia are difficult to correct even after correction of acidosis; therefore, hydrochlorothiazide administration at a dose of 0.5-1 mg/kg/day in divided doses every 12 h is recommended. With this measure, volume depletion from the extracellular space is achieved as well as an increase of calcium reabsorption in the proximal tubule. Adverse effects of treatment include hypotension, hyponatremia, hyperglycemia, and hypokalemia. In dietary terms, it is recommended to increase fruit and vegetable intake, which provide an alkalinizing diet.[68]

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