# Renal Tubular Acidosis in the Neonate

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## EDUCATION GAPS

Metabolic acidosis is a significant metabolic derangement that negatively impacts neonates. Clinicians who care for neonates should be able to recognize and understand the pathophysiology of renal tubular acidosis, a cause of metabolic acidosis.

## OBJECTIVES *After completing this article, readers should be able to:*

1. Describe acid-base homeostasis by the kidney.
2. Differentiate between the 3 major types of renal tubular acidosis (RTA).
3. Explain how to diagnose and treat RTA.

## ABSTRACT

Metabolic acidosis can manifest in the neonatal period and cause significant morbidity and mortality in neonates. Preterm infants are at an even higher risk of developing metabolic acidosis. If the acidosis results from a dysfunction of acid-base homeostasis by the renal system, the disorder is known as renal tubular acidosis (RTA). In this review, we will describe renal development and normal acid-base homeostasis by the renal system. We will also discuss the pathophysiology of the different types of RTA, laboratory findings to aid in diagnosis, and treatment considerations. Understanding RTA will help neonatal clinicians recognize and diagnose an infant affected by RTA and initiate treatment in a timely manner.



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**ABBREVIATIONS**

| | |
|---|---|
| ATPase | adenosine triphosphatase |
| $CO_2$ | carbon dioxide |
| dRTA | distal renal tubular acidosis |
| GFR | glomerular filtration rate |
| $H^+$-ATPase | hydrogen-ATPase |
| $H_2CO_3$ | carbonic acid |
| $H_2O$ | water |
| $HCO_3^-$ | bicarbonate ion |
| Na-H | sodium hydrogen |
| Na-$HCO_3^-$ | sodium bicarbonate |
| PHA | pseudohypoaldosteronism |
| pRTA | proximal renal tubular acidosis |
| RTA | renal tubular acidosis |

## INTRODUCTION

Metabolic acidosis is a common laboratory finding encountered in the neonatal period, especially in preterm infants. If the acidosis occurs as a result of a dysfunction of acid-base homeostasis by the renal system, the disorder is known as renal tubular acidosis (RTA). In this review, we will describe renal development and normal acid-base homeostasis by the renal system. We will also discuss the pathophysiology of the different types of RTA, laboratory findings to aid in diagnosis, and treatment considerations.

## ACID-BASE HOMEOSTASIS

A normal pH in arterial blood is 7.35 to 7.45. Maintenance of this systemic pH is important for metabolic functions and is therefore tightly regulated by

multiple buffers within the body. The main buffering system, known as the bicarbonate buffer system, functions through the regulation of bicarbonate ions ($HCO_3^-$) and carbon dioxide ($CO_2$). (1) The relationship between $HCO_3^-$ and $CO_2$ is explained by the following chemical equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

where $H_2O$ is water, $H_2CO_3$ is carbonic acid, and $H^+$ is hydrogen ions.

The pH of this buffer system is defined by the Henderson-Hasselbach equation as follows:

$$pH = 6.1 + \log \frac{[HOC_3^-]}{0.03 \ x \ pCO_2}$$

(6.1 represents the acid-dissociation constant of carbonic acid, 0.03 represents a solubility constant of $CO_2$ in the blood)

Changes in $P_{CO_2}$ are mainly dependent on alveolar minute ventilation.

## Bicarbonate Reabsorption in the Kidney

The kidneys play a major role in the regulation of $HCO_3^-$ concentration in the blood, and they accomplish this by means of the following 2 major functions: reabsorption of filtered $HCO_3^-$ and production of new $HCO_3^-$. (2)

In the kidney, $HCO_3^-$ is freely filtered at the glomerulus, and, thus, the concentration of $HCO_3^-$ in plasma and the ultrafiltrate is the same. In the proximal tubule, ~80% of the filtered $HCO_3^-$ is reabsorbed. This occurs via the actions of the sodium-hydrogen (Na-H) exchangers (NHE3) at the apical membrane of the renal epithelial cells in the proximal tubule and the sodium-bicarbonate ($Na\text{-}HCO_3^-$) cotransporter (NBCe1-A cotransporter) on the basolateral membrane of the same cells (Fig 1). (3) Na-H exchangers actively secrete $H^+$ into the lumen of the proximal tubule, which combine with filtered $HCO_3^-$ to form $H_2CO_3$ and ultimately $H_2O$ and $CO_2$. $CO_2$ diffuses across the apical membrane into the cell and combines with $H_2O$ by the action of intracellular carbonic anhydrases to form $H_2CO_3$, which, in turn, then forms $H^+$ and $HCO_3^-$ ions. Following this, $HCO_3^-$ is transported into the interstitial space along with sodium via the $Na\text{-}HCO_3^-$ cotransporter. Sodium-potassium pumps on the basolateral membrane keep the concentration of sodium within the proximal tubule cell low for these processes to function.

In the distal convoluted tubule and collecting ducts, $HCO_3^-$ is also reabsorbed, however, in limited capacity, as compared to the proximal tubule. Approximately 10% of filtered $HCO_3^-$ that is not reabsorbed in the proximal tubule is reabsorbed in the distal nephron. (4) Hydrogen ions that are transported into the lumen of the distal tubules also drive the generation of $HCO_3^-$, similar to the production of $HCO_3^-$ seen in the proximal tubules via the

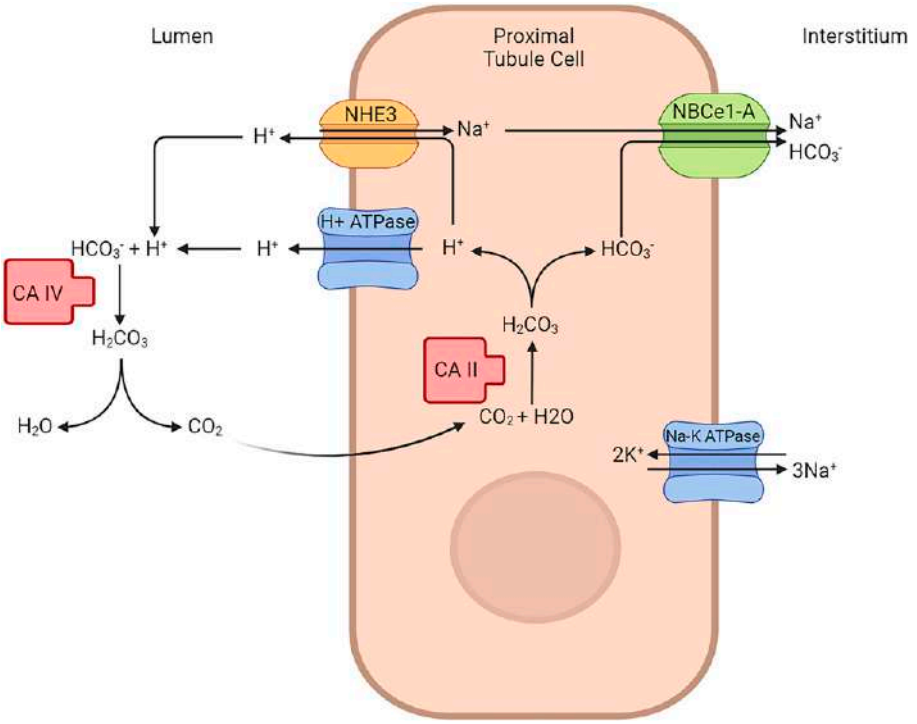


**Figure 1.** Bicarbonate reabsorption in the proximal tubule cell. Figure created with the aid of BioRender. ATPase=adenosine triphosphatase, CA II=carbonic anhydrase 2, CA IV=carbonic anhydrase 4, $CO_2$=carbon dioxide, $H^+$=hydrogen ion, $H_2CO_3$=carbonic acid, $HCO_3^-$=bicarbonate ion, $K^+$=potassium ion, $Na^+$=sodium ion, NBCe1-A=sodium bicarbonate cotransporter, NHE3=sodium-hydrogen exchanger.

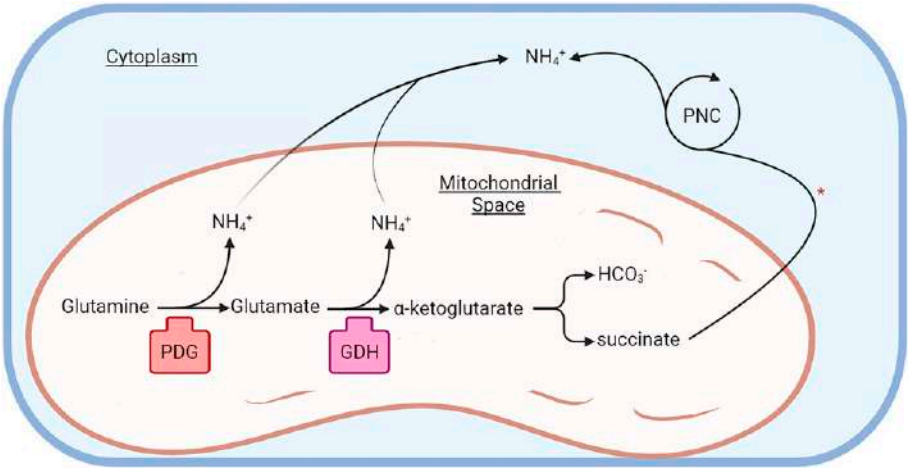


**Figure 2.** Ammoniagenesis. The majority of ammoniagenesis occurs in the mitochondrial space, in which glutamine is converted to glutamate and then to α-ketoglutarate, via the PDG and GDH enzymes, respectively. Further formation of ammonia occurs in the cytoplasm via PNC. Asterisk (*) refers to a simplification showing the byproduct of GDH and succinate, which undergoes multiple conversions before entering the PNC as aspartate. Figure created with the aid of BioRender. GDH=glutamate dehydrogenase, $HCO_3^-$=bicarbonate ion, $NH_4^+$=ammonium ion; PDG=phosphate-dependent glutaminase, PNC=purine nucleotide cycle.

action of intracellular carbonic anhydrase. The $HCO_3^-$ generated is then transported into the bloodstream via the chloride-bicarbonate exchanger AE1 and the Na-$HCO_3^-$ cotransporter NBCe1-A. (5)

### Excretion of Hydrogen

In addition to $HCO_3^-$ reabsorption in acid-base homeostasis, the kidney also plays a role in the excretion of $H^+$. The predominant mechanism of $H^+$ excretion is via the excretion of ammonium, which is not completely understood. (6) $H^+$ is buffered by ammonia in the urine, as well as in smaller amounts as other titratable acids such as phosphoric acid. (7) The majority of ammonia in the urine is generated rather than filtered via the glomerulus, in a process known as ammoniagenesis (Fig 2), in the renal epithelial cells. (8) While all segments of the nephron have the ability to form ammonia, most of this occurs in the proximal tubule. The main mechanism of ammoniagenesis involves the enzymes phosphate-dependent glutaminase and glutamate dehydrogenase. In the mitochondria, phosphate-dependent glutaminase converts glutamine into glutamate, which produces ammonium. Glutamate is then further metabolized into ammonium and α-ketoglutarate by glutamate dehydrogenase. This process also generates $HCO_3^-$, which is reabsorbed into the bloodstream. Another minor pathway that generates ammonia involves the metabolism of aspartate in the purine nucleotide cycle.

$H^+$ is also secreted in the distal tubules of the nephron and the collecting duct (Fig 3). On the luminal membrane of α-intercalated cells, hydrogen pumps actively transport $H^+$ into the lumen of the distal convoluted tubule, and hydrogen-potassium exchangers also transport $H^+$ into the lumen of the distal convoluted tubule. (4) These hydrogen ions then combine with ammonia and other titratable acids and are excreted in the urine.

## RENAL DEVELOPMENT OF THE FETUS AND FUNCTION IN THE NEWBORN

Fetal development of the kidneys, or nephrogenesis, begins with the formation of the ureteric bud, which is the precursor to the genitourinary system. (9) This occurs at ~5 weeks' gestation. The ureteric bud eventually divides into the structures that form the major and minor calyxes and the collecting ducts. Adjacent mesenchymal cells, known as the metanephric blastema, are invaded by the dividing ureteric bud and form the structures of the nephron, including the glomeruli and renal tubules. (9) Formation of nephrons continues until ~35 to 37 weeks' gestation and is generally complete at 38 weeks' gestation. Many factors influence the number of nephrons that are formed at birth, including fetal growth restriction, chorioamnionitis, genetics, and prematurity. (10) While the healthy adult kidney can contain a wide number of nephrons, ranging from 250,000 to more than 2 million nephrons, (10) the healthy term neonatal kidney contains ~1 million nephrons. (11) In neonates, there is a positive correlation between the weight and development of the neonatal kidney and the gestational age of the neonate (i.e., the older the gestational age of an infant, the greater the number of nephrons).

At birth, a full-term neonate has a glomerular filtration rate (GFR) approximately one-fifth or one-sixth of that of an adult, representative of the functional immaturity of the neonatal kidney. (11) Preterm infants have an even further decrease in

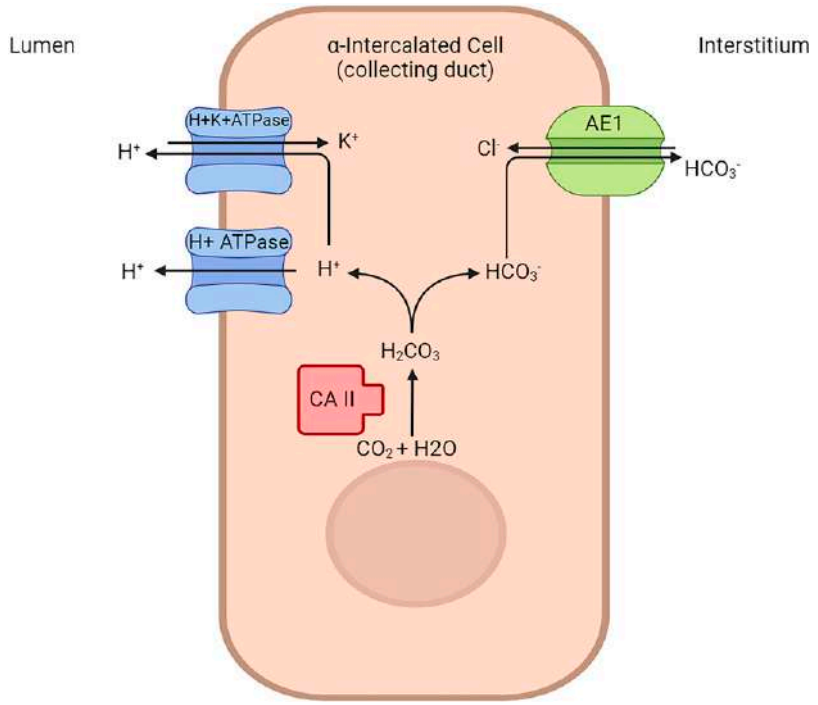


**Figure 3.** Hydrogen excretion. $H^+$ excretion in the α-intercalated cell of the collecting duct. $H^+$ is generated via intracellular CA II, and is secreted into the lumen of the collecting duct via hydrogen ATPases and hydrogen-potassium exchangers. The $HCO_3^-$ generated by CA II is transported into the bloodstream via the chloride-bicarbonate exchanger AE1. Figure created with the aid of BioRender. AE1=anion exchanger 1, ATPase=adenosine triphosphatase, CA II=carbonic anhydrase II, $CO_2$=carbon dioxide, $H^+$=hydrogen ion, $HCO_3^-$=bicarbonate ion, $H_2O$=water.

renal function. The GFR of a preterm infant at 32 to 34 weeks' gestation is ~14 mL/min per 1.73 $m^2$, compared to a term infant who has a GFR of 21 mL/min per 1.73 $m^2$. (9) This is a result of many potential factors. Preterm infants have immature kidneys as a result of incomplete nephrogenesis at birth, as well as immaturity of the renal vascular system, which leads to a lower renal perfusion pressure. (9) Preterm infants often have other medication complications including hypoxia, hypercapnia, acidosis, and hypotension, which may negatively impact renal function.

## RENAL TUBULAR ACIDOSIS

RTA is the impaired ability of the renal system to maintain a normal acid-base status, (7) either through an impairment in $HCO_3^-$ reabsorption or excretion of $H^+$, or both. Patients with all forms of RTA have hyperchloremic metabolic acidosis, with a normal anion gap. The pathophysiology and clinical signs and symptoms of the 4 types of RTA are discussed below (Tables 1 and 2).

### RTA Type I

RTA type I, or distal RTA (dRTA), is caused by a defect in acid excretion in the distal nephron, either because of impaired $H^+$ secretion or an increased permeability of the luminal membrane to $H^+$.

RTA type I can be caused by mutations in the gene *SLC4A1* that encodes the chloride-bicarbonate exchanger AE1, which is found on the basolateral membrane of cells in the

**Table 1.** Renal Tubular Acidosis (RTA)

| RTA Type | Primary Defect | Serum Bicarbonate | Serum Potassium | Urine pH | Urine Anion Gap |
|---|---|---|---|---|---|
| I (distal) | Defect in acid secretion | Low | Low or normal | Elevated (>5.5) | Positive |
| II (proximal) | Defect in bicarbonate reabsorption | Low | Low or normal | Usually <5.5, but variable depending on serum bicarbonate. | Negative |
| IV (hyperkalemic) | Mineralocorticoid deficiency or tubular aldosterone resistance | Normal | Elevated | <5.5 | Positive |

**Table 2.** Common Causes of Renal Tubular Acidosis (RTA) in the Neonatal Period

| RTA Type | Causes |
|---|---|
| I (distal) | Primary<br>• AE1 mutations (*SLC4A1*)<br>• Hydrogen-ATPase mutations (*ATP6V1B1*, *ATP6V0A4*)<br>Secondary<br>• Systemic lupus erythematosus<br>• Sjogren syndrome<br>• Amphotericin B |
| II (proximal) | Primary<br>• NBCe1-A (sodium-bicarbonate cotransporter) mutations<br>• Carbonic anhydrase mutations<br>• NHE3 (sodium-hydrogen exchanger) mutations<br>• Glycogen storage disease type I<br>• Hereditary fructose intolerance<br>• Galactosemia<br>• Tyrosinemia<br>• Dent's disease<br>• Lowe syndrome<br>• Renal immaturity<br>Secondary<br>• Carbonic anhydrase inhibitors |
| IV (hyperkalemic) | Aldosterone deficiency<br>• Congenital adrenal hyperplasia<br>o 21-hydroxylase deficiency<br>o 3-beta-hydroxysteroid dehydrogenase deficiency<br>o lipoid adrenal hyperplasia<br>• Congenital adrenal hypoplasia<br>• Aldosterone synthase deficiency<br>• Pseudohypoaldosteronism type II<br>Aldosterone resistance<br>• Psuedohypoaldosteronism type I<br>• Spironolactone |

collecting duct, (12) or mutations genes, which encode subunits of the hydrogen-ATPase ($H^+$-ATPase) *ATP6V1B1* and *ATP6V0A4*. (13) A mutation in AE1 causes an increase in intracellular $HCO_3^-$ in the distal tubule cells, which inhibits $H^+$ formation. Mutations in the $H^+$-ATPase prevent proper $H^+$ secretion into the lumen. A form of AE1 is also present on red blood cell membranes, and a defect in the encoding genes may also cause dRTA with hereditary spherocytosis or ovalocytosis. (12)(14) The *ATP6V1B1* and *ATP6V0A4* genes are also expressed in the cochlea and may lead to sensorineural hearing loss. (13)

Secondary causes of RTA type I include autoimmune disorders such as systemic lupus erythematosus and Sjogren syndrome, but these diagnoses are rare in neonates. Amphotericin B may cause dRTA as it increases the permeability of the luminal membrane to $H^+$.

dRTA may manifest clinically with nonspecific signs such as failure to thrive, poor feeding, hypotonia, and irritability. Biochemical analysis may show a nonanion gap metabolic acidosis, a low serum $HCO_3^-$ level, and elevated serum chloride. Urine pH may be abnormally elevated as well, typically with a pH of more than 5.5, with a decrease in urine ammonium and titratable acids. (15) A positive urine anion gap may also suggest a defect in ammonium excretion. (9) Hypercalciuria may result initially from metabolic acidosis, and nephrolithiasis may occur because of the precipitation of calcium phosphate in the urine.

## RTA Type II

RTA type II, or proximal RTA (pRTA), is caused by a defect in the maximum $HCO_3^-$ reabsorption by the proximal tubules. (9)(16) As a result, filtered $HCO_3^-$ above the lowered reabsorptive capacity is wasted via urine, at usually a serum $HCO_3^-$ level of ~15 mEq/L. (9) Of note, the proximal tubule has many functions, including the transport of phosphate, magnesium, amino acids, and glucose, and patients with pRTA may also have disorders relating to these separate functions.

The immaturity of the renal system seen in both term and preterm neonates may lead to a transient pRTA because of the inability to maximally reabsorb filtered $HCO_3^-$. (17) Term neonates have a reabsorptive capacity of 20 to 24 mEq/L $HCO_3^-$, whereas preterm neonates have a reabsorptive capacity of 15 to 24 mEq/L $HCO_3^-$. (9) Preterm newborns are at a higher risk of excessive solute wasting in the urine, including minerals, amino acids, and glucose. In addition, the preterm kidney is unable to concentrate urine maximally. (15)

pRTA can manifest as a result of a general dysfunction of the proximal tubule, which is known as renal Fanconi syndrome. This may be the result of various genetic causes or acquired causes, including inborn errors of metabolism such as glycogen storage disease type I, hereditary fructose intolerance, galactosemia, and tyrosinemia, in which pathologic accumulation of metabolites cause impairment in proximal tubule function. (18) Two X-linked recessive disorders that may cause pRTA are Dent disease and Lowe syndrome. Dent disease, because of a mutation in the *CLCN5* gene, affects proximal tubule hydrogen-chloride exchangers and the function of the $H^+$-ATPase, and patients may also have other electrolyte derangements, rickets, hypotonia, cataracts, and intellectual impairment. (19) Lowe syndrome, because of a mutation of the *OCRL1* gene, is an X-linked recessive disorder causing pRTA, and affected patients may also present with hypotonia, rickets, glaucoma, and neurodevelopmental delay. (20)

Other genetic causes of isolated pRTA include mutations in the NBCe1-A or in the carbonic anhydrase enzyme, (16)(21)

and mutations in the Na-H exchanger, NHE3. (22) These isolated defects in $HCO_3^-$ reabsorption are rare. A secondary cause of pRTA in the neonatal period is the use of carbonic anhydrase inhibitors such as acetazolamide, which can be used in infants with bronchopulmonary dysplasia.

Similar to dRTA, pRTA may manifest clinically as failure to thrive, poor feeding, hypotonia, and irritability. As pRTA is a defect in $HCO_3^-$ reabsorption, $HCO_3^-$ will be reabsorbed until it reaches the capacity of the neonate's proximal tubules. Affected patients have hyperchloremic, nonanion gap metabolic acidosis. (15) The urine pH may be normal if the proximal tubules have not reached their reabsorptive capacity of $HCO_3^-$; for example, if the tubular reabsorptive capacity is pathologically lowered to 15 mEq/L $HCO_3^-$, the urine will be appropriately acidified to a pH of 5.5 or less with a serum $HCO_3^-$ level of 14 mEq/L. Nephrolithiasis does not usually occur in patients with pRTA if the urine is appropriately acidified, which prevents the precipitation of calcium phosphate and promotes the formation of water-soluble calcium oxalate.

### RTA Type III

RTA type III is rare and appears in patients with mutations in carbonic anhydrase. (23) Patients have impairments in proximal tubule $HCO_3^-$ reabsorption, as well as a distal tubule inability to excrete acid. Because of its rarity, there is a paucity of information on this subtype, and it is poorly defined and rarely discussed in the context of neonates.

### RTA Type IV

The main defect in RTA type IV is a mineralocorticoid deficiency or a tubular aldosterone resistance. Normally, aldosterone activates mineralocorticoid receptors to increase the activity of the Na-H exchanger, NHE3, and the $H^+$-ATPase in the proximal tubules. It also increases the activity of sodium-potassium ATPases, sodium channels, and aquaporins in the distal nephron. The overall effect of aldosterone is to increase sodium reabsorption and potassium excretion. (24)(25)

After birth, neonates have a physiologic aldosterone resistance, which is manifested clinically as hyponatremia, hyperkalemia, and elevated levels of plasma aldosterone and renin. This aldosterone resistance is increased in preterm infants. (25) As a result, injuries to the renal system (ie, urinary tract infection) in the neonatal period have been associated with the development of transient type IV RTA, which is worsened in the presence of an underlying genetic disorder. (26)(27)

Neonates may have a mineralocorticoid deficiency as a result of congenital adrenal hyperplasia, as found in 21-hydroxylase deficiency, 3-beta-hydroxysteroid dehydrogenase deficiency, and lipoid adrenal hyperplasia. (28) In addition, preterm infants may have immaturity of the synthetic pathway of aldosterone, leading to hypoaldosteronism, which, in the absence of other disorders, improves by the third day after birth. (29) Genetic causes of mineralocorticoid deficiency include defects in the synthetic pathway of aldosterone, such as aldosterone synthase deficiency, (30) or developmental disorders, such as congenital adrenal hypoplasia. Pseudohypoaldosteronism (PHA) type 2, also called Gordon syndrome, is due to mutations in the *WNK1*, *WNK4*, *KLHL3*, and *CUL3* genes. (31)

PHA has an autosomal dominant or recessive pattern of inheritance and affected neonates have a resistance to aldosterone. Renal PHA type 1 is caused by a mutation in the *NR3C2* gene, which encodes for the mineralocorticoid receptors present in the distal tubules and collecting ducts; (32) systemic PHA type 1 is due to mutations encoding for the *ENaC* subunit genes. (33) Spironolactone may also cause an aldosterone resistance by competing with aldosterone for the aldosterone receptor.

Patients with type IV RTA may manifest clinically with failure to thrive, poor feeding, vomiting, dehydration, and lethargy. In addition, laboratory studies show hyponatremia, hyperkalemia, and metabolic acidosis. Patients with a mineralocorticoid deficiency have a lower plasma aldosterone level and increased adrenocorticotropic hormone levels, and patients with aldosterone resistance have increased aldosterone and cortisol levels and a decreased adrenocorticotropic hormone level.

## DIAGNOSIS

If RTA is suspected in an infant, a blood gas analysis needs to be conducted to confirm if there is metabolic acidosis, along with the screening of sodium, chloride, and $HCO_3^-$ levels to calculate the anion gap. As noted previously, neonates with all forms of RTA have hyperchloremic metabolic acidosis with a normal anion gap. Serum bicarbonate may be low in some forms of RTA or may be normal. Serum potassium may be low, normal, or elevated. (34) Other electrolytes that may be affected in RTA are calcium and phosphate.

Urine pH can be measured in patients with RTA and may be persistently elevated despite metabolic acidosis. The urine anion gap can be measured to estimate ammonia secretion and is calculated as urine sodium plus urine

potassium minus urine chloride, or urine (Na + K – Cl). Ammonium is excreted along with chloride, and if ammonium excretion is decreased, the urine anion gap will become more positive as less chloride will be secreted. The urine anion gap is normally positive, but it may be difficult to interpret in newborns because of a lack of normal values.

## MANAGEMENT

In general, patients with RTA should be treated with bicarbonate supplementation to correct the metabolic acidosis, and patients who present with failure to thrive or dehydration should also be given an adequate daily caloric intake and have fluid deficits corrected.

Patients with dRTA generally require lower doses of bicarbonate than patients with pRTA to maintain normal serum pH and $HCO_3^-$ levels. (9) In dRTA, correction of the metabolic acidosis and treatment of hypokalemia can be achieved with potassium citrate; oral solutions can be given starting at 2 to 3 mEq bicarbonate/kg per day. In pRTA, higher doses of bicarbonate, potentially reaching 15 mEq/kg per day, may be required. (35) Depending on the cause of the proximal tubule dysfunction, potassium, sodium, phosphate, and magnesium supplementation may also be required. (35) In patients with hyperkalemic RTA, all sources of potassium should be considered and discontinued if hyperkalemia is present. As with the other forms of RTA, patients should be given bicarbonate supplementation to correct the metabolic acidosis associated with hyperkalemic RTA. Depending on the cause of the RTA, mineralocorticoid replacement therapy may be indicated to correct the underlying cause.

## CONCLUSION

Metabolic acidosis is a potentially life-threatening condition in the neonate and has many causes. Understanding RTA as a cause of metabolic acidosis will allow for the timely diagnosis and treatment of neonates with this condition and can prevent serious morbidity or mortality. In the absence of any genetic disorder that may cause long-term morbidity, patients with RTA, if diagnosed and treated quickly, generally have a good long-term prognosis.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.
- Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants.
- Know how to manage metabolic acidosis and metabolic alkalosis in infants.

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