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Review Article

Renal Tubular Acidosis and Normal Anion Gap Metabolic Acidosis: A clinical review for General Medicine Physicians

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Abstract

Acidosis is a common clinical finding with serious consequences. Most of these disorders are due to high anion-gap metabolic acidosis or GIT causes. It's important to differentiate various types of metabolic acidosis due to differences in management and workup. Renal tubular disorders are not very common, but a significant number of these cases are lifelong and also need follow-up for ongoing monitoring. These disorders also have a significant long-term impact on patients' electrolytes, kidneys, and bones.

Many medical graduates and trainees find it hard to understand the underlying pathophysiology and tests used for diagnostic purposes. Additional difficulties in the management are faced due to the complex nature of these diagnostic approaches. There are often delays in the diagnosis due to the rarity, complexity, and overlapping nature of these disorders.

This review focuses on the various pathophysiological and clinical facts based on international guidelines. The purpose is to provide a clear understanding and approach to managing such cases.

Keywords: Normal anion gap metabolic acidosis, renal tubular disorders.

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Introduction

Normal Anion Gap Metabolic Acidosis (NAGMA): Acidosis (low pH) with normal anion gap is one of the following:

1. Renal Tubular Acidosis
2. Intestinal (Diarrhea, pancreatic fistula). These are more common than RTA but are relatively easier to identify due to the obvious clinical manifestations of the GIT disorder. However, the acidosis side of the picture may be overshadowed and overlooked due to dominant GIT issues.
3. Saline induced (high Chloride causing low HCO3 to keep total negative ions at the same level). This is an important but short-lived cause that can be easily corrected by judicious use of the appropriate quantity and type of fluids.[1]

Clinically Relevant Concepts and Tests

Plasma Anion Gap (AG): Anion Gap= (Na + K) – (Chloride + HCO3).

- AG is there as we don't measure all the anions in the blood (albumin, phosphate, etc.) to calculate all the anions. It's important to understand that this AG is only due to inadequate measurement of anions by the tests we use to assess acid-base, and in real-life human physigh anion gap acidosis. However, AG is affected by many anions that are not included/ measured for this calculation of AG. For example, albumin and other anions in the blood affect the anion gap. Secondly, the anion gap has a wide range. The normal anion gap for every individual would be expected to fall in the range, but it may be at the lower end or upper end of the range. For example, if patient A has a baseline AG of 8, when checked, even if the AG has increased to 13, it still falls within the range. Similarly, for those whose baseline AG is close to the upper limit of normal, just a 1–2-unit increment can make it look abnormal. This problem can only be solved if we know the baseline AG of the patient.[1,2]
- Coexisting high and normal anion gap is also possible. Such a case can easily miss normal anion gap acidosis in the presence of high anion gap acidosis. How-

ever, coexisting with two different types of acidosis often tips the pH very low, and HCO3 can also be very low.

Delta Gap: Delta gap detects AG with reference to the HCO3 and helps to assess such cases. Normal anion gap acidosis doesn't change AG but changes HCO3, whereas high anion gap acidosis often causes a 1:1 change in increasing AG & decreasing HCO3 (unless there is a gross disparity in the volume of distribution of HCO3 and the anionic part of the acid).

Delta Anion Gap= Actual Anion gap - ideal anion gap

Delta HCO3= Ideal HCO3- Actual HCO3.

Delta Anion Gap / Delta HCO3

- If the ratio is 1-2, it's metabolic acidosis
- If the ratio is less than 1, it's combined high anion metabolic acidosis and normal anion acidosis.
- If the ratio is more than 2, it's mixed Metabolic acidosis and respiratory acidosis.
- A low ratio means that HCO3 has reduced more than the Anion Gap, hence there should be some reason to explain this extra change in HCO3.
- A high ratio means HCO3 reduction is less than the change in AG, hence there should be a reason to explain this lesser change in HCO3 [2,3].

Urinary Ammonia and Acidosis: Acids (H-ions) in the renal tubules are neutralised by phosphate as H_2PO_4 (dihydrogen phosphate) and ammonia (Nh3). They share almost 50% burden in normal life. However, phosphate has a limited supply and cannot be increased. In the setting of systemic acidosis with increased demand to neutralize the acid (H+ Ions) in the tubules, ammonia (NH3) production is increased in the tubules (if the tubules are healthy). In patients with RTA or advanced-stage CKD, tubules can't increase NH3 production. Therefore, acidosis with high NH4 in the urine is extra-renal, whereas acidosis with low NH4 production in the urine is renal tubular.[1,2,3,4]

NH4 Measurement in Urine: Direct measurement in 24-hour urine

- Indirect measurement by measuring urinary osmotic gap &/or urinary anion gap (see later for details). A high osmotic gap means high ammonia in the urine (as ammonia is a strong osmotic agent). A negative urinary anion gap indicates high ammonia production.

Urinary Nh4 Interpretation in NAGMA;

NGMA with Urinary NH4 <40 mEq/day.

1) Neobladder, where NH4 gets absorbed into the blood. H/o bladder reconstruction surgery should be there.

2) Distal RTA / Mixed Distal & Proximal RTA.

3) Type IV RTA (Hyperkalemia due to lack of aldosterone, which suppressed NH3 production).

4) AKI or CKD.

NAGMA with Urinary NH4> 40 mEq/day:

1) Extra renal cause of normal anion gap acidosis (GIT, ureterosigmoidostomy, intestinal fistula)

2) Proximal RTA (type 2 RTA), or mixed proximal and distal RTA.

3) Euvolemic DKA can also have a normal anion gap.

Urinary Osmolar Gap: NH4, urea, glucose, and Na are all osmotic chemicals in the urine. Alcohol and its products are also osmotic in nature. Calculated osmolarity is always lower than the measured, as not all the osmotic chemicals are included in the formula.

Osmolar gap = Measured osmolarity -calculated osmolarity.

Calculated osmolarity= (Na + K) + (urea/2.8) + (glucose /18).

- Urea and glucose have 10 times weaker osmolarity than Na. Therefore, their quantity is divided by 1/10th of their molecular weight.
- High osmolarity gap: In the absence of glucose and alcohol, the osmotic gap is most likely due to high NH4. Therefore, the osmotic gap is an indirect measurement of urinary NH4 (with the assumption that there is no other reason for a high osmotic gap).
- Osmotic gap <150 means low NH4 & gap > 200 indicates high NH4.
- Limitations of Urinary Osmotic Gap & Acidosis: Osmotic gap is affected by alcohol and its products, glucose, urea, mannitol, and other osmotic agents. Osmotic gap is also affected by the presence of urease-positive organisms, which create NH4 from the urea. The osmotic gap of the urine in the absence of these confounders is mainly due to NH4. A rough estimate of urine NH4 in mEq / L is half of the urinary osmotic gap (mOsm). Extrarenal acidosis with appropriate renal tubular response increases the urinary osmolar gap >200 mOsm/L, and a similar gap is <150 mOsm/L, indicating an abnormal tubular response pointing toward the renal tubular acidosis.

Urinary Anion Gap (UAG): Formula for UAG = (Na + K)-(Chloride).

Increase NH3 production by the renal tubules increases chloride excretion in the urine (to maintain electrical neutrality of ammonium Nn4+). This increase in chloride in the urine reduces urinary anion gap (negative urinary anion gap). Whereas reduced ammonia synthesis by the tubular cells will also reduce chloride loss in the urine, causing low urinary chloride and increased urinary anion gap. Urinary anion gap is an indirect measure of renal tubular ammonia synthesis. A smaller or negative gap means more ammonia synthesis, and more gap means less ammonia synthesis.

In a patient with metabolic acidosis, tubules try to compensate by producing HCO3 & NH3, which are needed to compensate for acidosis. Therefore, if tubules are making more NH3 (indicated by reduced urinary anion gap) in cases of metabolic acidosis, it means tubular cells are functioning normally & acidosis is not due to tubular dysfunction. If renal tubular cells are not making ammonia (indicated by a high urinary anion gap) in a patient with metabolic acidosis, it means tubular cells are not fulfilling their responsibility and are likely the culprit to cause the acidosis.

Conclusion

- High (positive) UAG = Tubular defect is the cause of acidosis.
- Negative (low) UAG = Tubular cells are not the reason for acidosis and are trying to compensate for acidosis.
- Limitations of Urinary Anion GAP & Acidosis: However, urinary anion gap is affected by urinary electrolytes (diet, GFR, diuretics, serum level of electrolytes, and volume status, which determines reabsorption by proximal tubules). Urinary AG should be calculated when hypovolemia & serum levels of these electrolytes etc has been corrected to minimise these confounding factors. Anion gap is also misleading, as it links NH4 only with chloride. Whereas, in reality, NH4 is filtered with other anions as well, such as HCO3, phosphate, ketones, antibiotic metabolites, etc.[3,4,5]

Urinary pH: Urine pH is a measure of free Hydrogen in the urine. Urine pH is determined by many factors, including NH3 produced by tubular cells, serum K level (as it affects NH3 production), H-ions secreted by late distal tubules (aldosterone-stimulated), and types of solutes excreted in the urine. Ammonia (produced by the tubular cells) binds with free hydrogen in the urine and causes an alkaline pH of the urine. High serum K blocks NH3 synthesis and can cause acidic pH of the urine. Low serum K stimulates NH3 synthesis and causes an alkaline pH of the urine.

- Increased H-ion secretion by the late distal tubules (stimulated by aldosterone) causes acidic pH of the urine (due to increased free H-ions in the urine). This also has a higher TTKG (Trans Tubular Potassium Gradient is the difference of K in the tubules - K in the peritubular capillary blood, and is an indicator of aldosterone activity. Deceased H-ion secretions from the late distal tubules (due to lack of Aldosterone effect) cause alkaline pH of the urine. This has low TTKG (as less K is being secreted into urine).
- RTA -1 is a lack of only H-ion secretion in the urine (but loss of more K in the urine in place of H-ions) in the collecting tubules. Therefore, RTA -1 (Distal RTA) has alkaline urine pH.
- RTA-IV has a lack of H & K secretion in the urine at the collecting tubules. Therefore, in theory, it should cause an alkaline pH as fewer H-ions are being thrown in the urine. But as the K level in the serum is also high, which block NH3 synthesis by all the tubular cells (including proximal). Lack of NH3 synthesis fails to neutralise H-ions secreted by the tubular cells above the collecting tubules. These free H-ions, which are not being neutralised (due to lack of NH3), cause an acidic pH of urine.
- In proximal RTA (RTA II): as HCO3 is being lost in the urine (with no defect in H-ion secretin or NH3 synthesis), urine pH is alkaline when serum HCO 3 level is above 15. However, when serum HCO3 levels drop to below 15, filtration of HCO3 from the glomerulus is put on hold, leading to acidic urine pH. Therefore, patients with RTA-II have variable urine pH depending on the serum HCO3. When they are given soda bicarbonate urine becomes alkaline. Otherwise, urine pH is acidic.
- Urine acidification is a test done by giving NH4CL (0.1 g/kg). This normally causes acidic urine pH in cases where H-ion channels in the collecting tubules are functional (type II / proximal tubular RTA). It fails to acidify the urine if these channels are not functioning (type 1 RTA).
- Urine pH can be alkaline in a non-renal cause of metabolic acidosis due to overproduction of NH3 by the tubular cells (overcompensation), which binds free H-ions, and urine becomes alkaline. This is a less common condition, and mostly urine pH is acidic in systemic acidosis due to increased H-ion secretion.
- Infections and urine pH: Infections produce lactic acid by bacterial use of glucose and cause acidic pH.
- Urease producing organism split urea (which is present in the urine) and release NH3 (as each urea molecule has two NH3 attached to one Co2). This NH3 binds with free H+ ions in the urine, and the pH becomes alkaline. Therefore, a UTI with alkaline pH means the organism is Urease producing, such as Proteus.
- An alkaline pH of the urine causes calcium & uric

acid deposition. It reduces infections and also helps remove toxins such as many drugs, poisons, Haemoglobin, myoglobin, etc. Whereas acidic pH prevents deposition of calcium and urate but often promotes damage due to drugs & toxins.[3,4,5,6]

Ammonium Chloride (NH4CL) Challenge Test: NH4CL, given orally as 0.1 gram /kg, often causes acidic urine pH if the H-ion channels of the collecting tubules are functioning. As they are absent / non-functional in RTA -1, the NH4CL challenge fails to acidify urine in cases with type 1 (Distal) RTA. Patients with RTA 2 & 4 have normal urinary acidification with the NH4CL challenge test.

Bicarbonate Challenge Test: Soda bicarbonate makes urine alkaline in patients with RTA-2 (as the glomerulus will start filtering HCO3 in the urine when serum HCO3 is >15mEq, but proximal tubules can't reabsorb this filtered HCO3 in RTA2.

Distal RTA (RTA 1)

Distal RTA is defective secretion of H-ions by the collecting tubular cells into the urine. Normal anion gap metabolic acidosis with high urinary pH (>6.0), low urinary NH4 (<40 mEq/day) & low citrate secretion is found in all cases of distal RTA. Serum K may be low or high (depending on its subtype).

- Low citrate due to increased reabsorption by the proximal tubules in an attempt to compensate for acidosis. Citrate is like HCO3 and helps neutralise acid in the blood. This low citrate is found in all types of distal RTA (as proximal tubules are normal). Low citrate in the urine increases the risk of calcification (calcium becomes soluble by binding with citrate).
- *Low NH3 excretion in distal RTA:* Ammonia production is ok, but it isn't filtered in the urine as H-ions are not excreted in the urine. Therefore, urinary NH4 + is low in all types of distal RTA. Low NH4 is measured either as direct quantification in a 24-hour sample or reduced (negative) urinary anion gap or high urinary osmolarity gap. Distal RTA has a low osmotic gap (<150 mOsm/Kg) and low 24-hour urinary NH4 (<40 mEq/day).
- Nephrocalcinosis in distal RTA is due to alkaline urinary pH and low citrates.
- Bone disorders in the distal RTA are due to chronic acidosis.
- Failure to acidify urine within 6 hours of NH4CL ingestion (0.1 gram/kg) OR within 8 hours of fludrocortisone (1mg, given with 40 mg furosemide) is also a common finding in all cases of distal RTA. These two tests help differentiate Hyperkalemic distal RTA (type 1 RTA) from RTA 4 (later has normal response to NH4CL or fludrocortisone).

Distal RTA has three main types;

Classic Distal RTA: Normally, H-ions or K are secreted by cells of the collecting tubule in exchange for sodium reabsorption. H-ions are secreted (in exchange for Na) through H-ATPase channels. If this H-ATPase is defective, cells can't excrete H-ions in exchange for Na reabsorption. In these cases, only K is secreted in exchange for Na and causes hypokalemic distal RTA.

- Damaged cells or damaged / non-functional / abnormal H-ATPase is the mechanism in classic distal RTA.
- This is common with systemic diseases such as SLE, Sjogren, Sarcoidosis, and PBC. The likely mechanism in these cases is immune mediated defect of the H-ATPase in the collecting tubular cells.
- Renal calcification is likely a cause for distal RTA associated with sarcoidosis or nephrocalcinosis.

Distal RTA with high K (Voltage-dependent Distal RTA)

Decreased Na-reabsorption from the urine also reduces the electrical gradient and hence decreases H-secretion into urine (normally, urine in the tubules becomes negative when Na is reabsorbed and needs a positive ion (H or K) for maintaining electrical neutrality). Failure in this process also causes distal RTA, but this has a high K (as K is also not secreted by the tubular cells). So, this mechanism of distal RTA has high K (instead of low serum K seen in classic distal RTA, which loses K into the urine in place of H-ions).

- This type of distal RTA is due to medications, urinary obstruction, pyelonephritis, and sickle cell disease. Medications causing hyperkalemic distal RTA are Bactrim, pentamidine, triamterene, and amiloride, which block the sodium channels and stop Na reabsorption[6,7,8]

Distal RTA due to cell membrane failure: Distal RTA may also be due to increased H-ion reabsorption from the urine and is caused by increased permeability of the cell membrane for cations, including H-ions. This permeability is altered by Amphotericin B, which can interact with the cholesterol in the cell membrane and create micro gaps. Lithium can alter this permeability, as well.

Incomplete Distal RTA: These cases have alkaline urine and nephrocalcinosis but lack acidosis and have normal serum K and normal urinary NH4 & citrate. However, ammonium chloride (NH4CL) challenge or fludrocortisone would fail to acidify the urine. This is probably a compensated defect in the H-ATPase excretion[4,7]

Treatment of distal RTA: Treatment of distal RTA is bicarbonates (HCO3) or citrate as sodium or K-salts.

RTA 4 (Mineralocorticoid deficiency): It's a deficiency of aldosterone or its effect on the collecting tubules: It causes normal anion gap acidosis with salt wasting (sodium loss in urine), hypovolemia, and hyperkalemia. This high K inhibits ammonia synthesis from the proximal tubular cells and therefore urinary ammonia is also low. RTA 4 has some similarities to the hyperkalemic variant of the distal RTA (type 1 RTA) due to the following common findings:

- Normal anion gap renal tubular acidosis
- Hyperkalemia
- Low urinary ammonia

However, RTA 4 is different from the Hyperkalemic variant of distal RTA due to the following clinical clues:

- Hyponatremia and sodium loss with hypovolemia
- Acidic urine pH (lack of ammonia in the urine).
- Normal urinary acidification with NH4CL or fludrocortisone, as H-ATPase and H/K channels are structurally intact and functional.

Pathophysiology and causes of RTA4: How is aldosterone produced and functions?

Hypovolemia, low Na, and high K are common physiological mechanisms to stimulate renin-aldosterone. Decreased renal blood flow (such as heart failure or renal artery stenosis) is also a strong stimulus for the renin-aldosterone system. PGE2 produced by the macula densa cells stimulates renin production. Similarly, sympathetic nerves activating Beta-1 receptors on the JG cells are also a stimulus for renin production.

Renin activates the production of angiotensinogen from the liver, which is converted to A-I. This Angiotensin I is converted to angiotensin II by ACE in the lung capillaries. A-II then stimulate adrenal glands to produce aldosterone by using 21 and 11 alpha hydroxylase enzymes.

Aldosterone binds with its receptors on the collecting tubules to stimulate Na reabsorption and excretion of H or K (in exchange for Na)8,9,10.

Blockage at any point in the above system causes aldosterone deficiency and causes RTA4:

- PGE 2 synthesis is inhibited by NSAIDs
- Sympathetic nerves are damaged by autonomic neuropathy (diabetes, amyloidosis, etc).
- B-1 receptors are blocked by beta-blockers
- ACE is inhibited by ACE inhibitors
- Angiotensin II is inhibited by angiotensin receptor blockers (ARBs)
- Aldosterone production is affected by adrenal damage, adrenal enzyme inhibition (calcineurin inhibitors, heparin, ketoconazole), or adrenal enzyme deficiency seen in congenital adrenal hyperplasia.
- Aldosterone receptors by Spironolactone. Aldosterone receptor resistance is pseudo-hypoaldosteronism.
- Channels by Amiloride or triamterene.
- CKD commonly causes high renin and aldosterone. However, CKD in conditions known to cause autonomic neuropathy, such as diabetes, can also cause low renin production, leading to low aldosterone. This low renin production is due to reduced ability to produce PGE 2 caused by damage to macula densa cells, or low renin production due to damage to JG cells.

Response to aldosterone may be absent if the tubules are damaged or there is resistance of aldosterone receptor.

Proximal RTA (RTA 2): Proximal tubules absorb 75-80% of the HCO3 with the help of an enzyme (Carbonic Anhydrase) located at the apical side of the cells.

HCO3 Reabsorption from the Proximal Tubules

1. **Step 1:** Within the tubular lumen, filtered HCO 3 (from the glomerulus) binds with H-ion (secreted by the tubular cells) and becomes H2CO3. This acid splits into CO2 & water. This process is mediated by the enzyme Carbonic Anhydrase.
2. **Step 2:** Within the tubular cells, the CO2 is absorbed from the tubular lumen into the tubular cells. Within the tubular cells, this absorbed CO2 binds with H2O again to become H2CO3 (within the tubular cells)
3. **Step 3:** Within Tubular cells, H2CO3 splits again to H-ions and HCO3.
4. **Step 4):** From the tubular cells, HCO3 enters the blood along with Na (Sodium bicarbonate transporter located at the basal side of the cell membrane). The H-ions are thrown into the tubular lumen (in exchange for Na) and are ready to start step 1 again.
5. **Step 5):** Within the tubular lumen, this H-ion is secreted from the cells into the lumen, starting step 1 again by binding with the HCO3 filtered from the glomerulus.
6. Defect at any of the above steps, such as an issue with Carbonic Anhydrase or NBC1 (Na- HCO3 Channel), or damaged tubular cells loses HCO3 in the urine.

Stages of Proximal RTA

- **At the start:** HCO 3 loss in the urine causes systemic acidosis, low serum HCO3, increased urinary HCO3 (fractional excretion >15%), and alkaline urine pH. HCO3 loss promotes loss of Na &/or K (one positive loss for one negative ion loss in the urine).

Alkaline urine also predisposes to calcification.

- Ongoing Untreated Phase: When serum HCO3 is below 15, further HCO3 filtration is stopped. Now, urine becomes acidic, and there is no more K or Na loss. Acidosis affects bones and causes osteomalacia.
- Treatment Phase: When HCO3 is given to these patients to treat the acidosis, serum HCO3 goes above 15, and HCO3 filtration restarts, losing HCO3 in the urine and causing a clinical picture similar to phase 1 (start of the disease). High fractional excretion of HCO3 >15%, alkaline urine, and risk of calcification and loss of K &/or Na in urine (with HCO3).

Clinical Aspects of Proximal RTA:

- ***Bone Disease in Proximal RTA (RTA 2):*** Osteomalacia is due to chronic acidosis (H-ions replacing calcium in the bone). Proximal tubule disease can also affect vitamin D production.
- ***Nephrocalcinosis in type 2 RTA:*** Risk is high due to alkaline pH. However, if RTA 2 is a part of Fanconi syndrome, tubules fail to reabsorb citrate as well, which reduces the risk of nephrocalcinosis (as citrate binds with calcium to keep it soluble).
- Diagnosis can be confirmed clinically based on serum and urine chemistry. In case of doubt, NaHCO3 challenge is given, which confirms RTA 2 if urinary fractional excretion of HCO3 is >15%.
- Presence of amino aciduria, renal glycosuria (without diabetes), loss of phosphate, salt & water indicates RTA2 is part of Fanconi syndrome.
- Carbonic Anhydrase type II defect also involves H-ion secretion in distal tubules, causing a mixed proximal and distal RTA (previously named as RTA 3). Drugs such as anti-epileptics and acetazolamide block type II CA. Type II CA defects often cause brain calcification as well11.12.13.14.

Causes of RTA 2 (Proximal RTA):

Carbonic Anhydrase Inhibition

- Anti epileptics: Topiramate, Zonisamide, Valproate.
- Acetazolamide
- Zoledronic Acid
- *Antibiotics:* Aminoglycosides, rarely tetracyclines
- Anti-viral: Tenofovir
- Anti-fungal: Amphotericin B
- Anti-cancer: cyclophosphamide, cisplatin, Carbonic Anhydrase Deficiency, Defective NBC1 (sodium bicarbonate channel defect).
- Proximal tubular cell damage (Fanconi syndrome)

Treatment of RTA 2

- HCO3 replacement at much higher doses (almost 20 times higher than the dose used for Distal RTA).
- Monitoring and management of K & Na as well
- Bone protection and other supportive treatment for Falcon syndrome15-17.

Summary of NAGMA

Low pH, low CO2, low HCO3, and normal anion gap are the main findings shared by all NAGMA.

Table 1: *A few Important clinical differences in various subtypes of metabolic acidosis.*

Clinical Parameter	RTA (NAGMA)	GIT (NAGMA)	Non-RTA Acidosis (HAGMA)
AG	Normal	Normal	High
Urinary pH	Alkaline (1 & treated type 2) Acidic (4, & untreated type 2)	Acidic	Acidic Rarely alkaline
Urinary NH3	Low (except RTA 2 without Fanconi).	High	High
Urinary AG	High (due to low NH3)	Low or negative	Low or negative
Urinary osmolar gap	Low (due to low NH3)	High	High
Serum K	Low in 1 & 2 High in 4 and a variant of type 1.	Often low (GIT loss)	High (cellular shift)
NH4CL Challenge	No acidification in type 1	Not done	Not done
Bicarbonate Challenge	Alkaline urine in type II and increased FeHCO3 >15%.	Not done	Not done
Nephrocalcinosis	Common in types 1 & 2		
Bone disease in longstanding, untreated acidosis.	Common	Common	Common
Causes	Genetic Acquired: tubular disorders, drugs, toxins, and autoimmune disorders.	Chronic diarrhea, fistula,	Ketoacidosis, lactoacidosis, ESRD, Alcohol, Drugs, Toxins,

No GIT issues indicate a renal tubular cause. Low urinary NH4 <40 mEq/day also points renal tubular cause.

1. If Serum K: If it's high, it's either RTA 4 or a variant of distal RTA (RTA 1) with hyperkalemia. RTA 4 has acidic urine pH <5.3, whereas variants of distal RTA 1 have urine pH >6.0. If Serum K is low: It's either proximal RTA (RTA 2) or classic distal RTA (RTA 1): RTA 1 has a high urine pH>6.0, and RTA 2 has acidic urine pH <5.3 (when the RTA 2 patient is not on HCO3 replacement). RTA 2 can also have normal urinary NH4 (if it's not part of Fanconi syndrome).
2. Urinary NH4, Urine AG, Urine osmotic gap, and Urine PH help differentiate RTA further.
3. The ammonium chloride challenge test is rarely needed but can help differentiate RTA1 from RTA4.

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Authors' Contribution

AH: Conception.

JV: Design of the work.

AH, JV: Data acquisition, analysis, or interpretation.

JV: Draft the work.

AH: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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