Renal Tubular Acidosis: Core Curriculum 2025

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Renal tubular acidoses (RTAs) are a subset of non-anion gap metabolic acidoses that result from complex disturbances in renal acid excretion. Net acid excretion is primarily accomplished through the reclamation of sodium bicarbonate and the buffering of secreted protons with ammonia or dibasic phosphate, all of which require a series of highly complex and coordinated processes along the renal tubule. Flaws in any of these components lead to the development of metabolic acidosis and/or a failure to compensate fully for other systemic acidoses. Identification and diagnosis of RTA can be challenging, and the consequences of untreated RTA can be life-threatening. The use of serum and urinary indices can help elucidate the kidney's capacity to respond to acidemia, characterize these disturbances further, and guide treatment.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

The renal tubular acidoses (RTAs) are a group of disorders characterized by impaired acid excretion by the kidney. Pulmonary gas exchange is a necessary, albeit insufficient, component of acid-base homeostasis. It is responsible for the removal of 15,000 mmol CO_2 (volatile carbonic acids) each day generated from the metabolism of carbohydrates and fats. This physiologic system, however, is incapable of excreting nonvolatile acids. Under normal physiologic circumstances, the kidney must excrete 1 mmol/kg/day of nonvolatile (ie, noncarbonic) or fixed acids (primarily sulfuric acid) generated predominantly from the metabolism of thiol-containing amino acids (methionine, cysteine).

Free proton (H^+) excretion does not meaningfully contribute to the excretion of nonvolatile acid. Excretion of the daily nonvolatile acid as free H^+ is not possible because it would require the production of about 1,750 liters of urine output per day at the lowest urine pH of 4.5. Instead, elimination of the nonvolatile acid load is primarily achieved by the excretion of H^+ in the form of 2 urinary buffers: dibasic phosphate (HPO_4^{2-}) and ammonia (NH_3). In addition, maintenance of homeostasis requires the reabsorption of approximately 4,000 mmol of filtered bicarbonate per day.

Net acid excretion (NAE) includes the 3 principal processes that maintain acid-base balance: reclamation of filtered bicarbonate, buffering of protons by dibasic phosphate (HPO_4^{2-}), and buffering by ammonia. In this installment of *AJKD*'s Core Curriculum in Nephrology, we review normal proton and bicarbonate handling throughout the renal tubule, the perturbations that cause RTA, and the optimal methods for the evaluation and management of these disorders.

NAE is calculated by the following equation:

$$\mathrm{NAE} = \left(H_2PO_4^- + NH_4^+\right) - \left(HCO_3^-\right) - \left(OA^-\right)$$

where $H_2PO_4^-$ is monobasic phosphate, NH_4^+ is ammonium, HCO_3^- is bicarbonate, and OA^- is organic acid.

Physiologic Mechanisms of Acid Excretion in the Kidney

Under normal physiologic conditions, the vast majority of bicarbonate is reabsorbed in the proximal tubule. Protons from nonvolatile acid are buffered in the extracellular fluid by HCO_3^- as well as by intracellular buffers. Fixed acid is ultimately excreted as $H_2PO_4^-$ and NH_4^+, a process that replaces consumed HCO_3^-.

Dibasic phosphate is freely filtered, exerting its buffering capacity in the proximal and distal tubule. The pKa of the HPO_4^{2-}/$H_2PO_4^-$ buffer system is 6.8. Hence, about 90% of the buffering by HPO_4^{2-} occurs above a pH of 5.8. The 30-40 milliequivalents (mEq) of dibasic phosphate filtered each day account for the excretion of approximately one-half of the daily fixed acid load. The buffering activity of dibasic phosphate is historically referred to as titratable acid because it has been quantified by back titration of the urine to a pH of 7.40.

NH_4^+ is synthesized in the proximal tubular cells by deamination of glutamine to glutamate

and NH_4^+. It is transported into the interstitium in the thick ascending limb, substituting for potassium on the Na–K–Cl cotransporter (NKCC). NH_4^+ dissociates to ammonia in the medullary interstitium under the influence of a relatively higher pH. NH_3 subsequently diffuses via Rh proteins into the medullary collecting duct and is "trapped" in the increasingly acidic urine as NH_4^+. Approximately 30-40 mEq of nonvolatile acid is excreted per day as NH_4^+. In chronic metabolic acidosis, the production of NH_4^+ may increase to about 200 mmol per day. Systemic acidemia leads to a 2-fold rise in glutamine levels, which induces increased enzymatic production of NH_4^+ by phosphate-dependent glutaminase, glutamate dehydrogenase, and phosphenolpyruvate carboxykinase.

In this Core Curriculum, we describe the etiologies and pathophysiologic disturbances leading to RTA (Boxes 1-3; Fig 1). The rationale treatment of RTAs is discussed in the context of their pathophysiology.

Additional Readings

- Kamel KS, Halperin ML. *Fluid, Electrolyte and Acid-Base Physiology*. 5th ed. Elsevier; 2016. ★ESSENTIAL READING
- Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders*. 5th ed. McGraw-Hill; 2001. ★ESSENTIAL READING
- Unwin RJ, Capasso G. The renal tubular acidoses. *J R Soc Med*. 2001;94(5):221-225. doi:10.1177/014107680109400506

Identification of Non-Anion Gap Metabolic Acidosis

Case 1: *A 54-year-old woman with a history of chronic diarrhea is evaluated for hypokalemia. She has had 5 loose bowel movements per day for the past year. On physical examination, her vital signs are normal. She is euvolemic. Laboratory studies show sodium, 136 mEq/L; potassium, 2.8 mEq/L; chloride, 110 mEq/L; total CO_2, 16 mEq/L; serum urea nitrogen (SUN), 35 mg/dL; creatinine, 0.9 mg/dL; and glucose 90 mg/dL. Venous blood gas shows pH 7.29, pCO_2 of 30, and bicarbonate of 14.*

Question 1: Which of the following is the next best test to understand this patient's acid-base status?

(a) Repeat serum chemistry and blood gas due to discrepant bicarbonate values.
(b) Urinalysis to assess the urine pH.
(c) Quantitative assessment of urinary NH_4^+ excretion.
(d) Arterial, rather than venous, blood gas.

For the answer to this question, see the following text.

This patient has acidemia with a low serum bicarbonate and a normal anion gap of 10 mmol/L, consistent with non-anion gap metabolic acidosis (NAGMA). NAGMA can arise due to impaired renal acid excretion as well as extrarenal bicarbonate losses (ie, diarrhea). Quantification of urinary ammonium excretion through both indirect

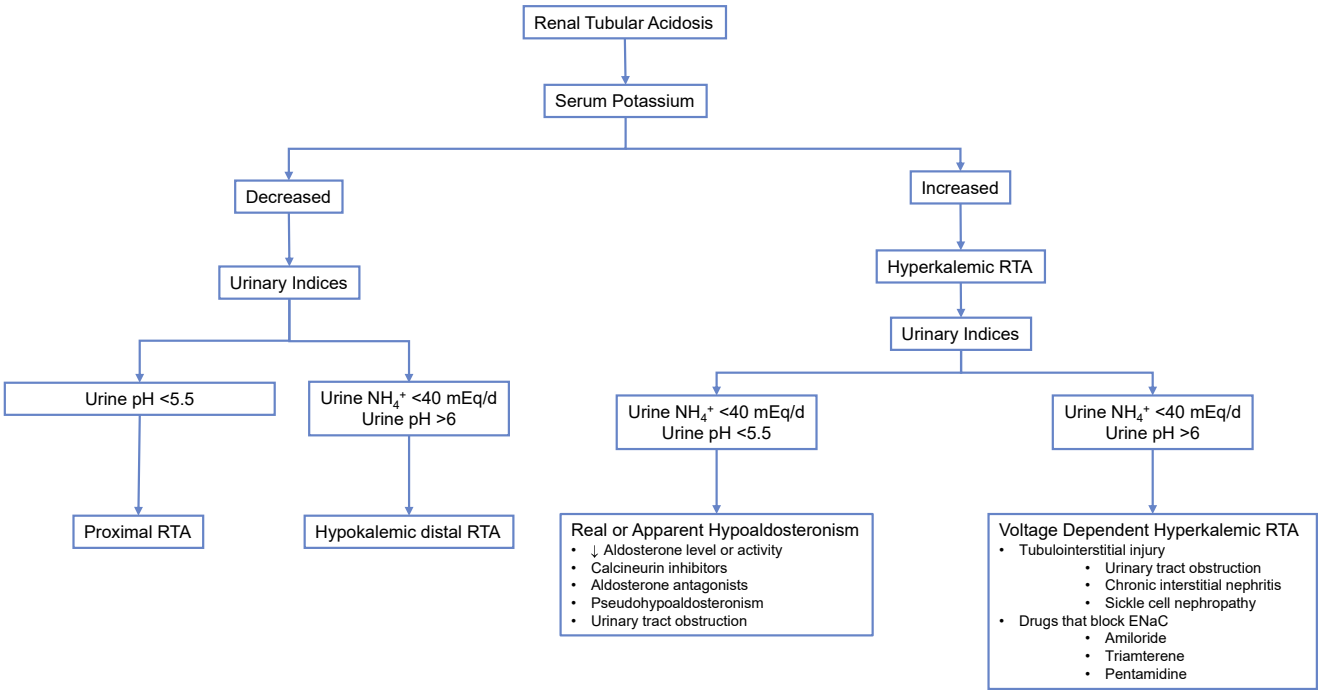

Figure 1. Classification of RTA. The RTAs are categorized by the presence of hypokalemia or hyperkalemia. The specific diagnosis of RTA is then derived from examination of the clinical phenotype in conjunction with analysis of urine pH and NH_4^+ excretion combined with adjunctive testing when indicated. Abbreviations: ENaC, epithelial sodium channel; NH_4^+, ammonium; RTA, renal tubular acidosis.

and/or direct methods is the next best step to diagnosis the etiology of NAGMA, so the answer is (c). Direct measurement of 24-hour urinary ammonium excretion is preferred. Measurement of the urine osmolal gap, while not perfect, can be used as a surrogate to assess urinary ammonium excretion. Urine pH can be used to differentiate various causes of RTA, but is not sufficient to further elucidate the cause of NAGMA based on the available information. Repeated measurement of the given parameters or obtaining an arterial blood gas is unnecessary. The slight difference between blood gas bicarbonate and serum total CO_2 measurement is expected, and in the majority of circumstances a venous blood gas is sufficient to assess acid-base status.

Although arterial blood gas (ABG) may provide the ideal measurement of systemic acid-base parameters, it requires either an indwelling arterial catheter or an arterial puncture. Available data suggest that the venous P_{CO2} is typically approximately 5-6 mm Hg higher than the arterial P_{CO2}, which is unlikely to be clinically significant. In patients with severe circulatory failure, this difference increases substantially. This patient does not have severe circulatory failure. Hence, there is no need to obtain an ABG.

The difference between bicarbonate values obtained via blood gas analyzers and total CO_2 measured by conventional serum chemistries (ie, a "basic metabolic panel" or "renal function panel") is minimal, expected, and rarely clinically significant. Whole blood analyzers directly measure pH and P_{CO2} and *derive* (rather than directly measure) the concentration of bicarbonate via the Henderson-Hässelbach equation. By contrast, some (not all) serum chemistry analyzers alkalinize the blood specimen in order to convert all CO_2 and carbonic acid into bicarbonate, which is then measured as "total CO_2." The bicarbonate ion makes up approximately 95% of total blood CO_2 content. Therefore, bicarbonate measured by blood gas analyzers is often slightly lower than the total CO_2 measured by on serum chemistry panels.

Following the identification of a metabolic acidosis, it is important to assess for the presence or absence of unmeasured anions (the "anion gap"), while simultaneously acknowledging the potential flaws of this measurement. First, the normal range of the serum anion gap is wide with a large standard deviation. The measurement of a patient's change in anion gap from baseline has been evaluated as a potential solution to address some of these challenges. Additionally, albumin is a key anion in the serum. Therefore, fluctuations in serum albumin as well as the charge ascribed to it can result in changes in the anion gap that are not due to underlying acidosis. Equations to estimate the effect of serum albumin on the anion gap have been proposed; however, despite these efforts, the anion gap is not a substitute or effective screening test for the direct measurement of clinically important anions such as β-hydroxybutyrate, lactate, or anions generated in the metabolism of toxic alcohols.

Although this review covers RTA, a subset of non-anion gap metabolic acidosis, it is important to recognize that NAGMA and high anion gap metabolic acidosis (HAGMA) can coexist. It is possible to estimate the proportion of acidemia attributable to one rather than the other by comparing the change in serum anion gap to the change in serum bicarbonate (termed the "delta-delta"). Each additional 1 mEq/L of a given unmeasured monovalent anion should decrease the serum bicarbonate by approximately 1 mEq/L to preserve electroneutrality whereas NAGMA will decrease the serum bicarbonate without increasing the serum anion gap. Unfortunately, this relies on accurate measurement of the anion gap, which is fraught with error as previously described. Furthermore, this is less reliable when the volume of distribution of the unmeasured anion is different from the volume of distribution of bicarbonate/protons (for example in lactic acidosis, in which the volume of distribution of protons is higher than that of lactate leading to a potentially elevated delta-delta).

While the anion gap and delta-delta remain important tools in the evaluation of metabolic acidosis, their use should be individualized, interpreted in the clinical context, and should not replace direct measurement of strong anions of concern when possible.

Additional Readings

- Androgue HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid-base status in circulatory failure. *N Engl J Med*. 2010;320(20):1312-1315. doi:10.1056/NEJM198905183202004
- Bihari S, Galluccio S, Prakash S. Electrolyte measurement: myths and misunderstandings—part II. *J Crit Care*. 2020;60:341-343. doi:10.1016/j.jcrc.2020.06.004
- Chong WH, Saha BK, Medarov BI. Comparing central venous blood gas to arterial blood gas and determining its utility in critically ill patients: narrative review. *Anesth Analg*. 2021;133(2):374-378. doi:10.1213/ANE.0000000000005501
- Fogh-Andersen N, Bjerrum PJ, Siggaard-Andersen O. Ionic binding, net charge, and Donnan effect of human serum albumin as a function of PH. *Clin Chem*. 1993;39(1):48-52. doi:10.1093/clinchem/39.1.48
- Kraut JA, Nagami GT. The serum anion gap in the evaluation of acid-base disorders: what are its limitations and can its effectiveness be improved? *Clin J Am Soc Nephrol*. 2013;8(11):2018-2024. doi:10.2215/CJN.04040413 ★ESSENTIAL READING
- Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol*. 2007;2(1):162-174. doi:10.2215/CJN.03020906
- Rastegar A. Use of the $\Delta AG/\Delta HCO_3^-$ ratio in the diagnosis of mixed acid-base disorders. *J Am Soc Nephrol*. 2007;18(9):2429-2431. doi:10.1681/ASN.2006121408

➢ Winter SD, Pearson JR, Gabow PA, Schultz AL, Lepoff RB. The fall of the serum anion gap. *Arch Intern Med*. 1990;150 (2):311-313. doi:10.1001/archinte.1990.00390140057012
➢ Witte DL, Rodgers JL, Barrett DA. The anion gap: its use in quality control. *Clin Chem*. 1976;22(5):643-646. doi:10.1093/clinchem/22.5.643

Diagnosis of Non-Anion Gap Metabolic Acidosis

Case 2: *A 19-year-old woman is referred for evaluation of hypokalemic metabolic acidosis. She developed increased leg weakness over the past week, eventuating in a fall. She has had intermittent loose stools over the past month. She has normal stature. On neurological examination, she has mild diffuse weakness in her legs. Laboratory studies show serum sodium, 142 mEq/L; potassium, 2.8 mEq/L; chloride, 118 mEq/L; total CO_2, 15 mmol/L; SUN, 14 mg/dL; creatinine, 1.1 mg/dL; albumin, 4 g/dL; and glucose, 96 mg/dL. A venous blood gas reveals pH 7.33 and P_{CO2} 36 mm Hg. Her urine chemistries are sodium, 62 mEq/L; potassium, 38 mEq/L; chloride, 56 mEq/L; creatinine, 110 mg/dL; urea nitrogen, 276 mg/dL; and osmolality of 338 mOsm/kg. Urinalysis shows pH 6.8; specific gravity, 1.008; trace protein; and negative blood and glucose.*

Question 2: Which of the following is the most likely diagnosis?

(a) Diarrhea
(b) Voltage-dependent RTA
(c) Proximal RTA
(d) Hypokalemic distal RTA

For the answer to this question, see the following text.

This patient has NAGMA as evidenced by the low pH, low venous P_{CO2}, a low serum bicarbonate level, and a calculated anion gap of 9 mmol/L. Identifying the cause of NAGMA requires differentiation of extrarenal losses of base versus a renal defect in acid excretion (Fig 2). The urine osmolal gap is 40 mOsm/kg, consistent with inadequate excretion of ammonium in response to systemic acidosis, excluding extrarenal loss of bicarbonate due to diarrhea. The low serum potassium level excludes voltage-dependent RTA. Finally, diminished NH_4^+ excretion favors hypokalemic distal RTA as the most likely diagnosis, so the correct answer is (d). Impaired α-intercalated cell proton excretion in the distal nephron in hypokalemic distal RTA causes decreased acid NAE and inappropriately low NH_4^+ excretion.

Identifying the Presence of RTA

RTA represents a spectrum of NAGMA characterized by impaired bicarbonate absorption or insufficient ammonium (NH_4^+) excretion. NAGMA may also occur due to extrarenal bicarbonate losses (ie, diarrhea), so quantifying urinary acid excretion is an import step in differentiating these 2 classes of acidosis. The urine pH can be used to *differentiate* certain types of RTA, but it is a representation only of the concentration of free protons ($[H^+]$) rather than a quantification of total acid excretion (which additionally includes ammonium ions and titratable acids).

Quantification of urinary NH_4^+ excretion has not been historically offered by commercial laboratories, despite being the ideal tool to assess ammonium excretion. However, quantitation of 24-hour urinary ammonium excretion is now increasingly available and should be used whenever possible. In the presence of systemic acidosis and the absence of a renal defect in urinary acidification, urinary ammonium excretion may rise to 200-300 mmol/day over the course of several days. This response is blunted in RTA as well as in chronic kidney disease (CKD). The urine osmolal gap, although not a direct measurement of ammonium excretion, is easily calculated and can be used to

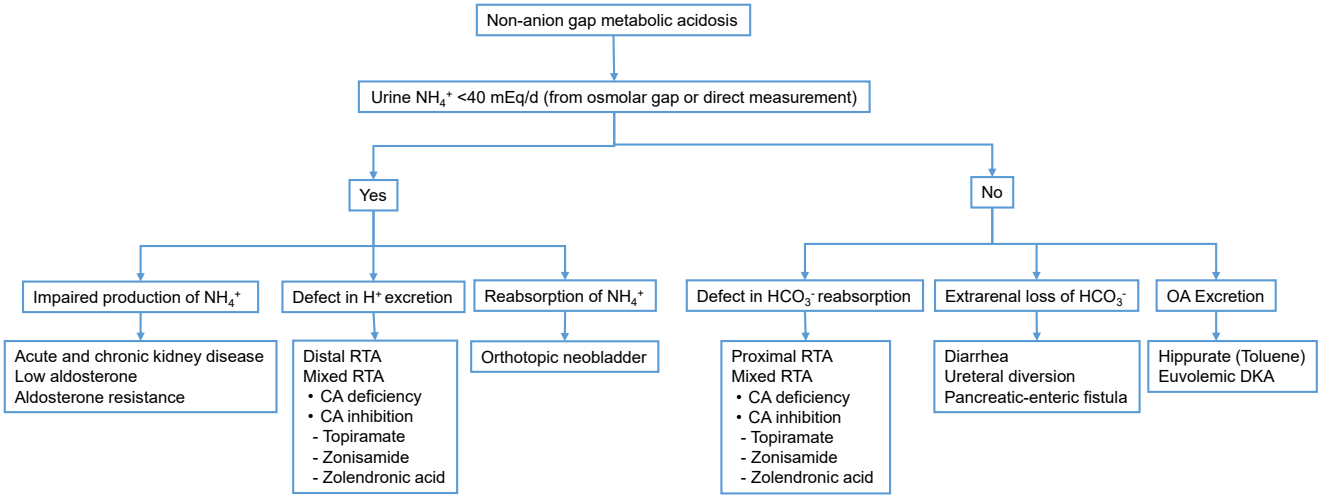

Figure 2. Diagnosis of non-anion gap metabolic acidosis. Abbreviations: CA, carbonic anhydrase; DKA, diabetic ketoacidosis; H^+, proton; HCO_3^-, bicarbonate; NH_4^+, ammonium; OA, organic acid; RTA, renal tubular acidosis.

qualitatively estimate NH_4^+ excretion as appropriate or inappropriate in a given clinical situation if direct spot or 24-hour ammonium excretion is not available.

The urine osmolal gap (Fig 3) represents the difference between the measured urine osmolality and calculated osmolality (Box 4). Ammonium is an important osmole in the urine and is accounted for in the measured urine osmolality. Ammonium excretion as an appropriate response to acidosis will increase the urine osmolal gap above 200 mOsm/kg because it contributes to the measured osmolality and not the calculated osmolality. Because ammonium salts make up the majority of the osmolal gap, ammonium concentration in mmol/L can be estimated to be approximately one-half of the urine osmolal gap in mOsm/kg. A low urine osmolal gap (<150 mOsm/kg) during metabolic acidosis represents inappropriately low ammonium excretion and the presence of RTA. This can be assessed even when other nonchloride anions are present as previously described. However, the urine osmolal gap may be falsely elevated in context of urease-producing microbes (due to elevated urea production) as well as the presence of other uncharged osmoles (mannitol, alcohols, glucose).

Although the urine anion gap (UAG)—the difference between the principal urinary cations (Na, K) and anions (Cl)—has been used to evaluate renal ammonium excretion, we do not recommend this approach. Theoretically, the UAG should be negative when ammonium excretion increases in systemic acidosis. However, a recent analysis suggested that the UAG is not a reliable index of urine ammonium excretion. In fact, there are myriad flaws associated with its use. First, ammonium excretion can increase to submaximal levels in proximal RTA. Therefore, assessment of urine ammonium excretion by calculation of the urine anion gap and osmolal gap is not helpful in differentiating between extrarenal losses of alkali (eg, diarrhea) and proximal RTA. In addition, the urine anion gap does not accurately reflect ammonium excretion when ammonium is excreted with nonchloride anions such as bicarbonate, ketone bodies, hippurate, and penicillin metabolites. Of note, proximal NaCl avidity due to hypovolemia can increase the UAG as well. Therefore, evaluation of RTA should occur after correction of hypovolemia. Lastly, UAG may be more representative of dietary intake rather than ammonium excretion.

In the upcoming sections, we elaborate on the use of these tests to distinguish between different types and etiologies of RTA.

Additional Readings

- Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. *N Engl J Med*. 1988;318(10):594-599. doi:10.1056/NEJM198803103181002
- Dyck RF, Asthana S, Kalra J, West ML, Lorne Massey K. A modification of the urine osmolal gap: an improved method for estimating urine ammonium. *Am J Nephrol*. 1990;10(5):359-362. doi:10.1159/000168150

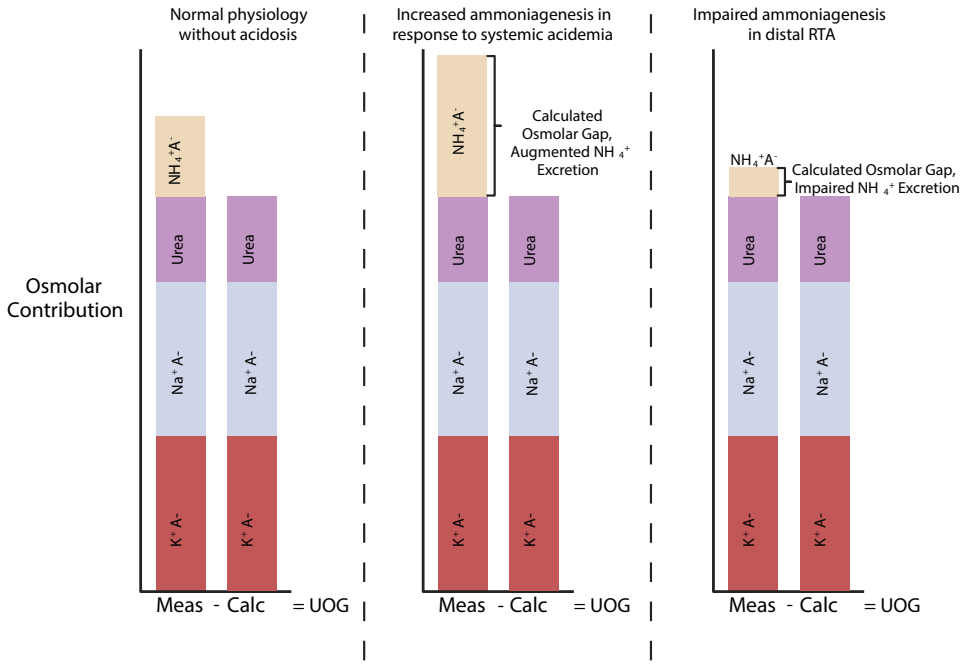

Figure 3. The urine osmolar gap in states of appropriate ammonium excretion and ineffective ammonium excretion. Abbreviations: A^-, anion accompanying cation as a salt; Calc, calculated osmolarity (see text for details); K, potassium; Meas, measured osmolarity; Na, sodium; NH_4^+, ammonium; RTA, renal tubular acidosis; UOG, urine osmolar gap. Created with BioRender.com.

- Kamel KS, Halperin ML. Use of urine electrolytes and urine osmolality in the clinical diagnosis of fluid, electrolytes, and acid-base disorders. *Kidney Int Rep*. 2021;6(5):1211-1224. doi:10.1016/j.ekir.2021.02.003 ★ESSENTIAL READING
- Kirschbaum B, Sica D, Anderson FP. Urine electrolytes and the urine anion and osmolar gaps. *J Lab Clin Med*. 1999;133:597-604. doi:10.1016/s0022-2143(99901 90-7)
- Marangella M, Formiconi A, Petrarulo M, et al. Time-related changes of metabolic and physicochemical profiles in patients with mechanical ileal neobladders. *BJU Int*. 2008;101(12):1571-1575. doi:10.1111/j.1464-410X.2007.07403.x
- Palmer BF, Clegg DJ. The use of selected urine chemistries in the diagnosis of kidney disorders. *Clin J Am Soc Nephrol*. 2019;14(2):306-316. doi:10.2215/CJN.10330818
- Raphael KL, Gilligan S, Ix JH. Urine anion gap to predict urine ammonium and related outcomes in kidney disease. *Clin J Am Soc Nephrol*. 2018;13(2):205-212. doi:10.2215/CJN.03770417
- Raphael KL, Yee J. It is really time for ammonium measurement. *Adv Chronic Kidney Dis*. 2018;25(4):297-300. doi:10.1053/j.ackd.2018.03.003
- Uribarri J, Goldfarb DS, Raphael KL, Rein JL, Asplin JR. Beyond the urine anion gap: in support of the direct measurement of urinary ammonium. *Am J Kidney Dis*. 2022;80(5):667-676. doi:10.1053/j.ajkd.2022.05.009 ★ESSENTIAL READING
- Uribarri J, Oh MS. The urine anion gap: common misconceptions. *J Am Soc Nephrol*. 2021;32(5):1025-1028. doi:10.1681/ASN.2020101509
- Yaxley J, Pirrone C. Review of the diagnostic evaluation of renal tubular acidosis. *Ochsner J*. 2016;16(4):525-530. https://pmc.ncbi.nlm.nih.gov/articles/PMC5158160/

Proximal Renal Tubular Acidosis

Case 3: *A 77-year-old woman is seen in consultation for hypokalemic metabolic acidosis. She was diagnosed with multiple myeloma 1 year ago and has responded to treatment with daratumumab, lenalidomide, and dexamethasone. Her course was complicated by a thoracic vertebral fracture and osteoporosis for which she has received treatment with zolendronic acid: 4 mg monthly for 3 months. Laboratory studies show that the λ light chain level has fallen from 24 mg/dL to the most recent level 1.82 mg/dL. Routine chemistries reveal serum sodium, 136 mEq/L; potassium, 3.5 mEq/L; chloride, 110 mEq/L; total CO_2, 16 mmol/L; SUN, 14 mg/dL; creatinine, 1.4 mg/dL (increased from a recent baseline level of 0.8 mg/dL); albumin, 3.9 g/dL; and glucose, 106 mg/dL. Prior chemistries had been within normal limits. Venous blood gas confirms a compensated metabolic acidosis. Her urinalysis shows pH 5.0; specific gravity, 1.015; trace protein; and 2+ glucose; her urine sodium is 112. Her vital signs are all within normal limits. She is started on sodium bicarbonate tablets. When she returns for her follow-up visit, her serum bicarbonate level is 18 mEq/L; potassium, 2.5 mEq/L; and urine pH 7.0.*

Question 3: Which one of the following is the most likely diagnosis?

(a) Primary aldosteronism
(b) Proximal RTA
(c) Hypokalemic distal RTA
(d) Hyperventilation
(e) Laxative abuse

Question 4: Which one of the following is the most likely cause for the AKI, hypokalemia, and metabolic acidosis?

(a) Myeloma-related light chain tubulopathy
(b) Daratumumab
(c) Zolendronic acid
(d) Lenalidomide

For the answers to these questions, see the following text.

This patient likely has proximal RTA, answer (b) to Question 3. Impaired reabsorption of bicarbonate in the proximal tubule leads to bicarbonate wasting until a new steady-state level is achieved, at which point bicarbonate wasting no longer occurs. With treatment, however, the serum bicarbonate exceeds the threshold for maximal reabsorption characteristic of proximal RTA, leading to bicarbonaturia. As a result, the urine pH rises to >6.0. Increased sodium bicarbonate delivery to the distal tubule in the presence of volume contraction and hyperaldosteronism accelerates sodium reabsorption by principal cells, and this generates greater lumen electronegativity and potassium wasting.

Zolendronic acid has been reported to induce proximal tubular injury and proximal RTA, so (c) is the correct answer to Question 4. Although myeloma may be associated with light chain proximal tubulopathy, it is unlikely that this patient would develop proximal tubulopathy while responding well to treatment. Daratumumab and lenalidomide are not known to cause proximal RTA.

Most of the filtered bicarbonate (75%-80%) is reabsorbed in the proximal tubule (Fig 4). The secretion of protons in the proximal tubules reacts with filtered HCO_3 to form H_2CO_3, which then dissociates to H_2O and CO_2. These reactions are catalyzed by carbonic anhydrase IV (CAIV) which is linked to the brush border of the proximal tubular cells. The CO_2 moves from the lumen back into the cell (mainly via the aquaporin channels). Each proton that is secreted into the lumen is associated with an ion of HCO_3 entering the blood via sodium bicarbonate cotransporter 1 (NBC1). Thus, proton secretion in this tubule segment is equivalent to HCO_3 reabsorption—or more accurately "reclamation."

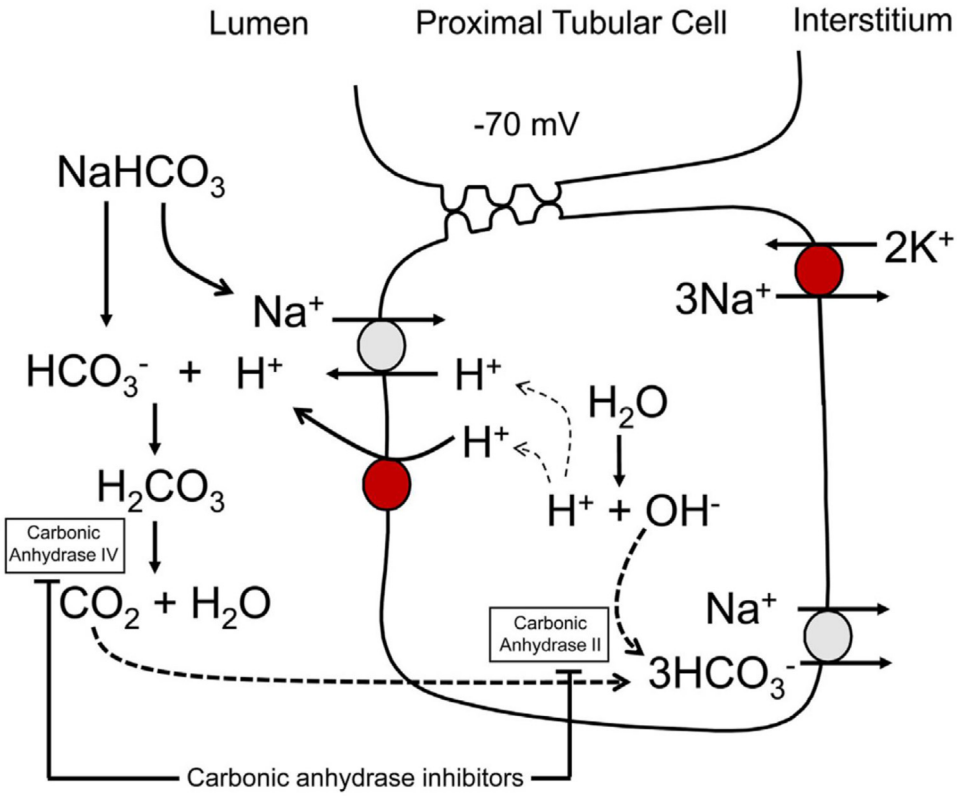

Figure 4. Role of carbonic anhydrase II and IV in the reabsorption of sodium bicarbonate in the proximal tubule. Abbreviations: CAIV, carbonic anhydrase IV; CO_2, carbon dioxide; H^+, hydrogen ion; H_2CO_3, carbonic acid; HCO_3^-, bicarbonate; H_2O, water. Reproduced with permission of the copyright holder (Elsevier) from Palmer BF, Clegg DJ. Respiratory Acidosis and Respiratory Alkalosis: Core Curriculum 2023. *Am J Kidney Dis*. 2023;82(3):347-359. doi:10.1053/j.ajkd.2023.02.004

Impairment in either apical proton secretion or carbonic anhydrase activity leads to incomplete reabsorption and excretion of a small proportion of filtered bicarbonate. Complete failure of bicarbonate reabsorption would be lethal because it would result in massive bicarbonate wasting and severe acidemia. Instead, the threshold of maximal absorption of bicarbonate in proximal RTA is lowered from 26 mmol/L to about 16-18 mmol/L. When bicarbonate supplementation raises the serum bicarbonate level above this threshold, the kidney will fail to reabsorb all of the filtered bicarbonate, leading to bicarbonaturia. Proximal RTA is typically associated with generalized proximal tubule dysfunction known as Fanconi syndrome. However, it can also result from isolated transporter dysfunction/variant (eg, NBC1), carbonic anhydrase dysfunction/deficiency, or drug-induced carbonic anhydrase inhibition. Common etiologies are summarized in Box 1.

Notably, carbonic anhydrase II deficiency (an autosomal recessive syndrome of osteopetrosis and RTA and brain calcification) affects both proximal tubule bicarbonate reabsorption and distal tubule proton excretion, thereby causing mixed proximal and distal RTA, previously termed a "Type III" RTA. This is extremely rare and results in a debilitating congenital syndrome starting in infancy. In addition, topiramate, zonisamide, and acetazolamide are all inhibitors of CAII and may cause acquired mixed RTA.

Identification of proximal RTA can be challenging because the urinary chemistries change considerably during treatment as well as in context of the underlying etiology. Conceptually, abrupt onset of proximal RTA is characterized by an initial loss of the resorptive capacity of bicarbonate, resetting the threshold of maximal absorption at a lower bicarbonate level. Initial bicarbonaturia occurs with several downstream effects that manifest with an initial increase in urine pH, increased distal sodium delivery and flow with associated kaliuresis. As the serum bicarbonate level falls to the lower maximum tubular resorptive capacity for bicarbonate ($Tmax_{HCO3}-$), filtered bicarbonate can be completely reabsorbed, restoring normal potassium handing and a urine pH that is <5.5. During treatment with bicarbonate supplementation or during a postprandial alkaline tide, serum bicarbonate increases once again, resulting in recurrence of hypokalemia and alkaline urine.

Nephrolithiasis can also occur with bicarbonaturia due to an elevated urinary pH. However, in Fanconi syndrome, there is often concomitant impaired citrate absorption, which can increase calcium solubility (as opposed to isolated proximal RTA in which acidemia-associated

Box 1. Selected Causes of Proximal (Type 2) RTA With or Without Fanconi Syndrome

Medications
- Topiramate
- Acetazolamide
- Zonisamide
- Tenofovir disoproxil fumarate
- Aminoglycosides
- Valproic acid
- Ifosfamide
- Zolendronic acid

Systemic Disorders
- Paraproteinemia (amyloidosis, multiple myeloma, light chain deposition disease)
- Toxic ingestion: heavy metals, aristolochic acid
- Sjogren's syndrome
- Hypocalcemia

Genetic Disorders
- Cystinosis
- Wilson disease
- NBC1 variant
- Lowe syndrome
- Fanconi-Bickel syndrome
- Dent disease

Abbreviations: NBC1, sodium bicarbonate cotransporter; RTA, renal tubular acidosis.

hypocitraturia increases stone risk). Regardless of the presence or absence of bicarbonaturia, chronic metabolic acidosis may result in osteomalacia due to the reabsorption of calcium and phosphate buffer compounds from the bone. In addition, proximal tubular dysfunction may lead to decreased synthesis of 1,25-dihydroxy-vitamin D.

Confirmatory testing for proximal RTA is rarely needed because the alkali load needed for treatment is markedly higher than distal or type 4 RTA. In circumstances in which the diagnosis is in doubt, the presence of proximal RTA can be confirmed by an inappropriately high (>15%) fractional excretion of bicarbonate ($FEHCO_3$) in response to an alkali load. Abnormally high excretion of amino acids, uric acid, phosphate, or glucose may signify the presence of Fanconi syndrome and diffuse impairment of proximal tubule anion reabsorption rather than isolated dysfunction.

Treatment of proximal RTA is centered on replacing the excreted bicarbonate, typically requiring as much as 20 mEq/kg/day. This can be done through a variety of formulations, including sodium bicarbonate tablets, sodium or potassium citrate, and baking soda. Hypokalemia should be corrected before starting bicarbonate replacement therapy because treatment results in bicarbonaturia and resultant kaliuresis as previously described. Unfortunately, efforts to replace renal bicarbonate losses with oral bicarbonate are often ineffective.

Additional Readings

- Faubel S, Topf J. *The Fluid, Electrolyte and Acid-Base Companion*. Alert and Oriented; 1999. ★ESSENTIAL READING
- Mirza N, Marson AG, Pirmohamed M. Effect of topiramate on acid-base balance: extent, mechanism and effects. *Br J Clin Pharmacol*. 2009;68(5):655-661. doi:10.1111/j.1365-2125.2009.03521.x
- Portales-Castillo I, Mount DB, Nigwekar SU, Yu EW, Rennke HG, Gupta S. Zoledronic acid-associated Fanconi syndrome in patients with cancer. *Am J Kidney Dis*. 2022;80(4):555-559. doi:10.1053/j.ajkd.2021.12.015
- Rastegar A, Soleimani M. Fluid, electrolytes, and acid base disturbances. *Nephrol Self Assess Program*. 2015;14(1):1-107.
- Soleimani M, Rastegar A. Pathophysiology of renal tubular acidosis: core curriculum 2016. *Am J Kidney Dis*. 2016;68(3):488-498. doi:10.1053/j.ajkd.2016.03.422
- Wesson DE. The importance of recognizing and addressing the spectrum of acid stress. *Adv Chronic Kidney Dis*. 2022;29(4):364-372. doi:10.1053/j.ackd.2022.06.001
- Whyte MP. Carbonic anhydrase II deficiency. *Bone* 2023;169:116684. doi:10.1016/j.bone.2023.116684

Distal Renal Tubular Acidosis

Case 4: *A 32-year-old woman with a history of ulcerative colitis is referred for recurrent nephrolithiasis. She was diagnosed with ulcerative colitis 2 years ago after developing frequent episodes of bloody diarrhea. After initiation of mesalamine, her stools have decreased in frequency to about 2 to 3 loose stools per day. Over the past 5 years, she has had 3 episodes of symptomatic nephrolithiasis. Her blood pressure is 130/80 mm Hg, and her heart rate is 76/min. There is no postural drop change in her blood pressure or pulse. There is no edema. She has not had recurrent urinary tract infection, weight loss, or rash. Laboratory studies show sodium, 140 mEq/L; potassium, 3.2 mEq/L; chloride, 100 mEq/L; total CO_2, 19 mmol/L; SUN, 12 mg/dL; creatinine, 1.1 mg/dL; calcium, 9 mg/dL; phosphorus, 2.6 mg/dL; and parathyroid hormone, 60 pg/mL. A urinalysis shows specific gravity 1.014, pH 6.8, negative leukocyte esterase, negative protein, negative glucose, and negative blood. Urinary indices show sodium 80, mEq/L; potassium, 42 mEq/L; chloride, 96 mEq/L; urea, 275 mg/dL; and osmolality, 372 mOsm/kg. A cross-sectional image from a computed tomography scan of the abdomen without contrast is shown in* Figure 5.

Question 5: Which of the following is the next best step in the diagnostic evaluation of this patient?

(a) Bicarbonate loading test
(b) 24-Hour metabolic stone panel
(c) Ammonium chloride loading test
(d) No further testing

Question 6: Which of the following is the most likely cause of this patient's acidosis?

(a) Diarrhea
(b) Proximal RTA
(c) Hypovolemia

(d) Distal RTA

Question 7: Which of following is the most likely composition of this patient's kidney stones?

(a) Calcium oxalate
(b) Uric acid
(c) Magnesium ammonium phosphate
(d) Calcium phosphate

For the answers to these questions, see the following text.

Distal RTA is distinguished by an inability of the α-intercalated cells to secrete protons, resulting in impaired urine acidification (elevated urine pH) and insufficient ammonium excretion (urine osmolal gap < 150 mOsm/kg) or 24-hour urine ammonium excretion < 40 mEq/day, as discerned from a 24-hour from a 24-hour metabolic stone panel, so answer (b) is correct for Question 5. The calculated urine osmolality is $2 \times (122) + 275/2.8 = 342$ mOsm. Hence, the urine osmolal gap is $372 - 342 = 30$ mOsm/kg. The estimated urine ammonium concentration is 15 mEq/L, or about 20-30 mEq per day, well below the minimal level of >40 mEq/d expected with the normal physiologic response to systemic acidemia. Urine ammonium excretion should be higher than 40 mEq/d and may rise to 200 mEq/d when there is gastrointestinal loss of bicarbonate and metabolic acidosis in diarrheal states. Therefore, diarrhea is not the predominant cause of this patient's acidosis. Ammonium excretion increases to submaximal levels in proximal RTA and usually exceed 40 mEq/d. Urine pH is generally <5.5 in proximal RTA in individuals who are not receiving alkali treatment. Therefore, proximal RTA is unlikely in this patient. Hypovolemia can lead to decreased delivery of sodium to the cortical collecting duct, leading to an inability to generate a lumen negative electropotential. As a result, proton excretion is impaired and may lead to metabolic acidosis and hyperkalemia. This patient has hypokalemia and no evidence of hypovolemia on physical examination. In addition, her urine sodium concentration is >40 mEq/L. The answer to question 6 is therefore (d).

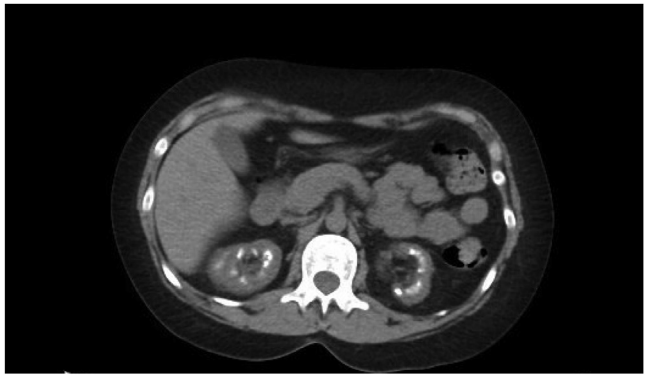

Figure 5. Computed tomography scan of the abdomen without contrast.

Box 2. Selected Causes of Distal (Type 1) Renal Tubular Acidosis

Classic Distal Renal Tubular Acidosis
- Sjogren syndrome
- Systemic lupus erythematosus
- Nephrocalcinosis
- Primary biliary cirrhosis
- Sarcoidosis

Voltage-Dependent Distal Renal Tubular Acidosis
- Triamterene
- Amiloride
- Pentamidine
- Trimethoprim sulfamethoxazole
- Urinary tract obstruction
- Sickle cell nephropathy
- Chronic pyelonephritis

Membrane Failure
- Amphotericin B
- Lithium

Genetic Disorders

Proton secretion (and therefore generation of bicarbonate) occurs in the distal tubule and requires several distinct steps. First, sodium is reabsorbed via epithelial sodium channels (ENaC) on the apical surface of principal cells, which generates a negative luminal charge and a more favorable electrochemical gradient for proton excretion. Maintenance of this gradient is critical, because the proton concentration difference between the tubular lumen and epithelial cells is significant. Proton excretion subsequently occurs via the H^+-ATPase in the α-intercalated cells as well as ATP-dependent H^+/K^+ exchangers. Bicarbonate generated during this process is reabsorbed into the systemic circulation (Fig 6).

Inability to generate a more negatively charged tubular lumen via electrogenic sodium reabsorption results in a lesser gradient available to drive H^+ secretion, a pathophysiologic state termed a "voltage-dependent distal RTA." Alternatively, a "classic distal RTA" results from impaired proton secretion due to dysfunction or possibly destruction of the H^+ ATPase. Given the importance of maintaining this gradient across the tubular basement membrane, increasing the permeability to tubular cations can result in back-diffusion of protons, a type of distal RTA seen due to antifungal therapy with amphotericin or with chronic lithium therapy. Additional causes of distal RTA are listed in Box 2.

The essential pathophysiologic defect in distal RTA leading to impaired NAE is the inability to secrete H^+ despite adequate ammonia production, leading to impaired ammonium excretion and elevated urine pH. Hypokalemia is common in "classic" RTA, potentially due to distal potassium secretion (to preserve tubule electroneutrality in lieu of proton secretion), impaired potassium reabsorption in the thick ascending loop of Henle, or sodium wasting and resultant secondary hyperaldosteronism. In contrast,

hyperkalemia is typical of voltage-dependent RTA because both potassium and hydrogen secretion are impaired due to the relatively positive tubular lumen. Nephrocalcinosis is a common manifestation of increased calcium reabsorption, alkalinization of the interstitium, and hypocitraturia. Nephrolithiasis (predominantly calcium phosphate in composition) may occur as well, owing to combination of high urine pH and acidemia-induced citrate reabsorption in the proximal tubule; the answer to question 7 is therefore (d). Similar to proximal RTA, bone loss may occur to buffer against chronic metabolic acidosis.

An entity termed "incomplete distal RTA" has been described in patients with high urine pH and recurrent calcium phosphate stone formation. These patients do not have NAGMA, and typically have preserved ammonium excretion, 2 features that are contrary to the diagnosis of true distal RTA. Various phenotypes of urine acidification and ammoniagenesis have been proposed, highlighting the gaps in the understanding of this disease. It is clear, however, that these patients will have an abnormal response to ammonium loading and furosemide/fludrocortisone testing (described below) similar to complete distal RTA.

An ammonium chloride loading test can confirm distal RTA when the diagnosis is uncertain, such as in cases of incomplete distal RTA. In the ammonium chloride loading test, 0.1 g/kg of ammonium chloride is administered by mouth. The urine pH is assessed 6 hours later using a pH meter. Distal RTA is most likely present if the urine pH fails to fall to <5.3. Ammonium chloride can induce nausea and vomiting; therefore, this test is seldom used. Instead, 24-hour urine excretion of citrate and ammonium can be assessed, both of which are reduced in distal RTA. One additional option is the furosemide-fludrocortisone test. Individuals with distal RTA are unable to lower the urine pH to <5.3 over the course of 8 hours following oral dosing of furosemide, 40 mg, and fludrocortisone, 1 mg. To note, the furosemide-fludrocortisone test is not well-validated, and 24-hour assessment of ammonium and citrate excretion is preferred.

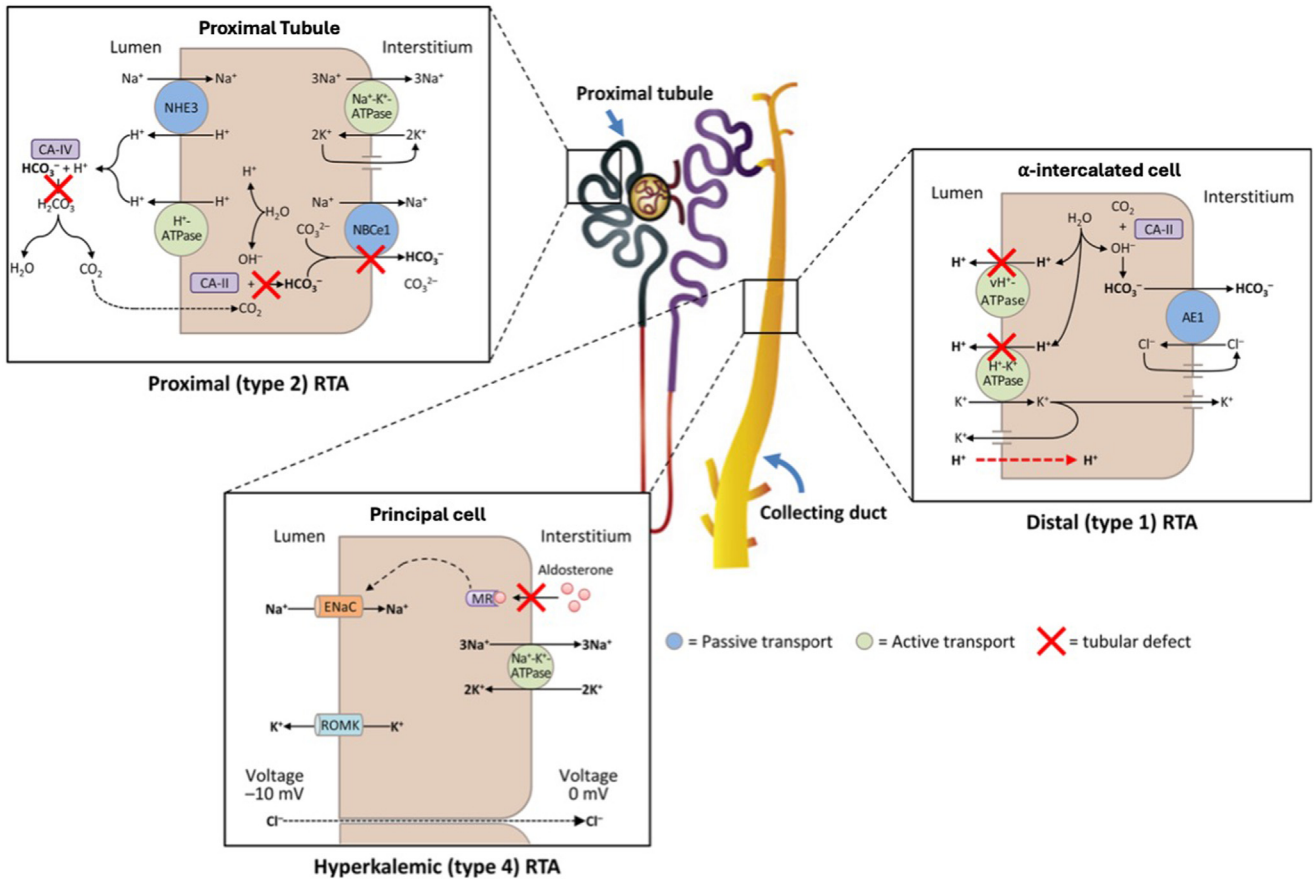

Figure 6. Pathophysiologic basis for proximal, distal, and type 4 RTAs. Abbreviations: AE1, kidney anion exchanger 1; CA-II, carbonic anhydrase II; CAIV, carbonic anhydrase IV; CO_2, carbon dioxide; ENaC, epithelial Na^+ channel; H^+, hydrogen ion; H_2CO_3, carbonic acid; HCO_3^-, bicarbonate; H_2O, water; MR, mineralocorticoid receptor; NBCe1, electrogenic sodium bicarbonate cotransporter 1; NHE3, sodium–hydrogen antiporter 3; H^+-ATPase, hydrogen-exporting ATPase; ROMK, apical membrane K^+ channel; RTA, renal tubular acidosis. Adapted from Palmer BF, Kelepouris E, Clegg DJ. Renal tubular acidosis and management strategies: a narrative review. *Adv Ther.* 2020;38(2):949-968. doi:10.1007/s12325-020-01587-5. Released under a Creative Commons BY-NC license.

Treatment of distal RTA focuses on alkali replacement. The daily dose needs to be sufficient to replace the daily acid load, which is typically 1 mmol/kg/day. Potassium containing salts are preferable in patients with hypokalemia. Unlike potassium bicarbonate, potassium citrate does not increase gastric carbon dioxide liberation and may be better tolerated.

Additional Readings

- Batlle D, Arruda J. Hyperkalemic forms of renal tubular acidosis: clinical and pathophysiological aspects. *Adv Chronic Kidney Dis*. 2018;25(4):321-333. doi:10.1053/j.ackd.2018.05.004 ★ESSENTIAL READING
- Dhayat NA, Gradwell MW, Pathare G, et al. Furosemide/fludrocortisone test and clinical parameters to diagnose incomplete distal renal tubular acidosis in kidney stone formers. *Clin J Am Soc Nephrol*. 2017;12(9):1507-1517. doi:10.2215/CJN.01320217
- Kurtz I. Renal tubular acidosis: H^+/base and ammonia transport abnormalities and clinical syndromes. *Adv Chronic Kidney Dis*. 2018;25(4):334-350. doi:10.1053/j.ackd.2018.05.005
- Wagner CA, Unwin R, Lopez-Garcia SC, Kleta R, Bockenhauer D, Walsh S. The pathophysiology of distal renal tubular acidosis. *Nat Rev Nephrol*. 2023;19(6):384-400. doi:10.1038/s41581-023-00699-9
- Walsh SB, Shirley DG, Wrong OM, Unwin RJ. Urinary acidification assessed by simultaneous furosemide and fludrocortisone treatment: an alternative to ammonium chloride. *Kidney Int*. 2007;71(12):1310-1316. doi:10.1038/sj.ki.5002220

Type 4 RTA

Case 5: *A 62-year-old man with long-standing type 2 diabetes mellitus is seen in consultation for increased albuminuria. He is feeling well and has no concerns. His vital signs are within normal limits with the exception of a blood pressure of 144/92 mm Hg. His medications are lisinopril, empagliflozin, semaglutide, and metformin. The laboratory evaluation demonstrates the following: His urinalysis shows pH 4.8; trace protein; 2+ glucose; and negative blood. His urinary albumin-creatinine ratio is 434 mg/g. A kidney ultrasound shows no hydronephrosis, and the postvoid residual bladder volume estimated at 25 mL.*

	Today	Reference Range
Sodium, mEq/L	137	136-145
Potassium, mEq/L	5.6	3.5-5.0
Chloride, mEq/L	106	98-106
Bicarbonate, mEq/L	19	23-30
SUN, mg/dL	14	8-20
Creatinine, mg/dL	1.2	0.7-1.2
Glucose, mg/dL	144	70-99
Plasma renin activity, ng/mL/h	4	0.6-3
Serum aldosterone, ng/dL	2	2-5
Hemoglobin A_{1c}, %	5.8	4.8-5.6

Question 8: Which of the following is the most likely diagnosis?

(a) Type 4 RTA
(b) Diabetic ketoacidosis
(c) Voltage-dependent distal RTA
(d) Hyporeninemic hypoaldosteronism

Question 9: In addition to dietary potassium restriction, which one of the following is best next step in management?

(a) Stop lisinopril.
(b) Start chlorthalidone.
(c) Start insulin.
(d) Start patiromer.

For the answers to these questions, see the following text.

This patient has a type 4 RTA most likely due to lisinopril, so the answer to Question 8 is (a). The diagnosis of type 4 RTA is supported by the presence of a non-anion gap metabolic acidosis, hyperkalemia, and a urine pH that is less than 5.5. Lisinopril decreases the production of aldosterone by inhibiting the conversion of angiotensin I to angiotensin II. As a result, aldosterone synthesis is impaired, leading to inappropriately low serum aldosterone levels in the presence of hyperkalemia. Decreased aldosterone levels stimulate renin due to loss of negative feedback of angiotensin II on renin release. Hence, plasma renin levels are slightly increased in response to treatment with angiotensin-converting enzyme inhibitors as noted in this patient.

Hyperkalemia impairs proximal ammonia generation with resultant impairment in NAE. If the hyperkalemia persists after discontinuation of lisinopril, hyporeninemic hypoaldosteronism due to diabetic kidney disease would remain a diagnostic consideration. Voltage-dependent distal RTA may occur in the setting of urinary tract

Box 3. Selected Causes of Type 4 Renal Tubular Acidosis

Medications
- Renin-angiotensin-aldosterone system blockade
  - o β-Adrenergic receptor blockers
  - o Angiotensin-converting enzyme inhibitors
  - o Angiotensin II receptor blockers
  - o Mineralocorticoid receptor antagonists
  - o Direct renin inhibitors
- Nonsteroidal anti-inflammatory drugs
- Calcineurin inhibitors
- Heparin and heparin analogues

Systemic Disease
- Chronic kidney disease
- Diabetes mellitus
- Primary adrenal insufficiency

Genetic Disorders
- Congenital hypoaldosteronism (21-hydroxylase deficiency and isolated hypoaldosteronism)
- Pseudohypoaldosteronism type 2 (Gordon's syndrome)

Box 4. Equations Used in the Assessment of Acid-Base Disorders and Renal Tubular Acidosis

$$\text{Serum anion gap} = \text{Serum } [Na^+] - \text{Serum } [Cl^-] - \text{Serum } [HCO_3^-]$$

$$\text{Delta gap or "delta-delta"} = \frac{\Delta\text{Serum Anion Gap}}{\Delta\text{Serum } [HCO_3^-]}$$

$$\text{Serum anion gap corrected for albumin} = \text{Serum Anion Gap} + (2.5 \times (4 - [\text{Albumin}(g/dL)])$$

$$\text{Urine Anion Gap} = \text{Urine } [Na^+] + \text{Urine } [K^+] - \text{Urine } [Cl^-]$$

$$\text{Urine Osmolal Gap} = \text{Measured Osmolality} - 2 \times (\text{Urine } [Na^+] + \text{Urine } [K^+]) + \frac{\text{Urine}\left[\text{Urea}\left(\frac{mg}{dL}\right)\right]}{2.8}$$

obstruction, but the findings on kidney ultrasound exclude obstruction. In addition, the urine pH would be expected to be >6.0 in distal RTA. Of note, urinary tract obstruction can also cause hyporeninemic hypoaldosteronism and type 4 RTA. The normal anion gap and lack of any significant symptoms makes the diagnosis of euglycemic diabetic ketoacidosis secondary to empagliflozin unlikely.

With regard to this patient's management, chlorthalidone would treat this patient's hypertension while also lowering his potassium, so the answer to Question 9 is (b). The contraction of the extracellular fluid volume would stimulate enhanced bicarbonate reabsorption in the proximal tubule, which could potentially counterbalance the metabolic acidosis. Lisinopril should be continued given this patient's proteinuric CKD and hypertension. Although transcellular potassium shifts and hyperkalemia can be caused by hyperglycemia, this patient's glucose is not high sufficiently enough by itself to warrant enhanced diabetes therapy. In addition, the patient does not have evidence of euglycemic diabetic ketoacidosis that would warrant treatment with insulin. The severity of the hyperkalemia and the likelihood that addition of a thiazide diuretic will correct the hyperkalemia weighs against the use of potassium binders such as patiromer or sodium zirconium cyclosilicate.

Type 4 RTA occurs due to relative mineralocorticoid deficiency or resistance, with a resultant decrease in electrogenic sodium reabsorption (less stimulation of basolateral Na/K ATPase and apical ENaC), impaired proton excretion due to reduction in apical H^+-ATPase activity, and subsequent hyperkalemia. Chronic hyperkalemia reduces ammonia production in the proximal tubule, which results in urine pH < 5.5 despite relative impairment in H^+-ATPase activity. Box 3 notes common etiologies of type 4 RTA. It is important to recognize that the combination of renal tubular acidosis and hyperkalemia is not limited only to type 4 RTA but is also seen in voltage-dependent distal RTA as mentioned earlier. The key differentiating factor is that distal proton secretion and urinary acidification are preserved in type 4 RTA, unlike voltage-dependent distal RTA.

Additional Readings

- Harris AN, Shankar M, Melanmed M, Batlle D. An update on kidney ammonium transport along the nephron. *Adv Kidney Dis Health*. 2023;30(2):189-196. doi:10.1053/j.akdh.2022.12.005
- Palmer BF, Kelepouris E, Clegg DJ. Renal tubular acidosis and management strategies: a narrative review. *Adv Ther*. 2020;38(2):949-968. doi:10.1007/s12325-020-01587-5 ★ESSENTIAL READING

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