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Pseudo-Renal Tubular Acidosis: Conditions Mimicking Renal Tubular Acidosis

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Pseudo-Renal Tubular Acidosis: Conditions Mimicking Renal Tubular Acidosis

Junior Uduman and Jerry Yee

Hyperchloremic metabolic acidosis, particularly renal tubular acidosis, can pose diagnostic challenges. The laboratory phenotype of a low total carbon dioxide content, normal anion gap, and hyperchloremia may be misconstrued as hypobicarbonatemia from renal tubular acidosis. Several disorders can mimic renal tubular acidosis, and these must be appropriately diagnosed to prevent inadvertent and inappropriate application of alkali therapy. Key physiologic principles and limitations in the assessment of renal acid handling that can pose diagnostic challenges are enumerated.

Key Words: Hyperchloremic metabolic acidosis, Renal tubular acidosis, Pseudo-RTA, Respiratory alkalosis, Urine anion gap

INTRODUCTION

Renal tubular acidosis (RTA) encompasses a spectrum of disorders caused by the inability of the kidneys to conserve bicarbonate or adequately excrete an acid load. In the evaluation of low serum bicarbonate and normal anion gap, RTA is within the spectrum of differential diagnoses considered.[1] Aside from selective population-based studies, RTA has a low prevalence in the adult population.[2,3] Nevertheless, RTA is a diagnosis frequently considered by trainees who are often perplexed by the diagnostic challenges. Interestingly, in 1992, the pediatric neurologist Donald Lewis postulated that the child-protagonist Tiny Tim of the 1843 Dickens' classic, *A Christmas Carol*, had type 1 or distal renal tubular acidosis (dRTA). Lewis arrived at his vatic conclusion based on Tim's symptomatology and available therapeutics at that time, which included "alkali."[4] Although understanding of the pathophysiology of RTAs has considerably advanced, the diagnosis of RTA still requires a meticulous and algorithmic assessment of clinical, laboratory, and urinary parameters. Additional complexity may be encountered by the multiple, validated approaches that are available.[1,5,6]

RTA is classically categorized into type 1, 2, and 4. Proximal RTA (type 2) can be congenital or acquired, resulting in proximal tubular injury/dysfunction and subsequent bicarbonaturia. Proximal RTA is frequently associated with Fanconi syndrome, and this disorder usually becomes apparent by the variable presence of glycosuria, aminoaciduria, calciuria, uricosuria, phosphaturia, and low-molecular-weight proteinuria.[7] In contrast, dRTA typically presents without overt clues and requires a systematic approach for successful diagnosis. The omission of vital diagnostic steps can mislead to an erroneous diagnosis of dRTA. The hallmark of dRTA is the presence of hyperchloremic metabolic acidosis (HCMA) and limited urinary net acid excretion.[5] Classic features include a urine pH greater than 6, renal potassium wasting, and diminished urine net acid excretion, which is manifested by a "positive" urine anion gap (UAG). The evaluation of RTA should be established during steady state conditions, when patients are in the outpatient setting. Pseudo-RTA is often a (mis)diagnosis made in the inpatient setting when diagnostic principles are misapplied. Using clinical scenarios, we aim to illustrate clinical mimics of dRTA for which treatment by alkali would be erroneous.

PATIENT SCENARIO 1

An 80-year-old female with a history of degenerative joint disease presented to the emergency room with altered mental status. She was afebrile, and her heart rate was 80 beats per minute, respiratory rate was 28 breaths per minute, and blood pressure was 112/70 mm Hg. Her admission laboratory examination revealed the following serum values: sodium (Na^+) 139 meq/L, potassium (K^+) 3.5 meq/L, chloride (Cl^-) 118 meq/L, total carbon dioxide (tCO_2) 12 meq/L, blood urea nitrogen 12 mg/dL, and creatinine 1.02 mg/dL.

Hypobicarbonatemia

Close attention to history and physical examination findings is likely to yield a diagnosis in most acid-base disturbances. The hyperventilation is a vital clue in assessing the acid-base disorder of this individual, in which hypobicarbonatemia and hypocapnia are the predominant features. Low serum bicarbonate may be the consequence of metabolic acidosis (increased anion or normal anion gap) with loss or titration of bicarbonate or a renal adaptive response to respiratory alkalosis.[8] An arterial blood gas establishes the diagnosis of respiratory alkalosis, negating the possibility of the misdiagnosis of hypobicarbonatemia attributable to a HCMA. The arterial blood gas of the patient showed a pH 7.70, PCO_2 10 mm Hg, and calculated bicarbonate 12 meq/L. Further workup revealed an elevated salicylate level of 63 mg/dL, thereby establishing the diagnosis of salicylism. Renal mitigation of the alkalinizing effect of the depressed PCO_2 demands a decrement of serum bicarbonate, the extent to which it is predictable, depending on whether the duration of hypocapnia is acute

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(<48 hours) or chronic (>48 hours). Because the pH of the patient is extreme, validation of the blood gas is recommended, and the following equation, a modification of the Henderson-Hasselbalch equation, can accomplish this task.[8]

$$pH = 7.62 - LOG_{10}\left(\frac{PCO_2}{[HCO_3^-]}\right)$$

After rearrangement and applying rules of logarithms, the equation is used to solve for bicarbonate, given the 2 most precise terms of the blood gas, which are the pH and PCO_2. The solution of the equation yields a bicarbonate value that closely approximates to that of the reported value. Accordingly,

$$[HCO_3^-] = \frac{PCO_2}{10^{(7.62-pH)}} = \frac{10}{10^{(7.62-7.70)}} = 12 \text{ meq/L}$$

The initial temporizing response occurs within minutes and is mediated through tissue and blood buffers. Hemoglobin and plasma proteins account for approximately one-third of this compensatory response. An additional contribution to buffering proceeds via tissue release of protons. Overall, the decline in bicarbonate concentration is a proportional response to the decrement in PCO_2.[9] We refer to the clinical scenario of pure, acute respiratory alkalosis with hypobicarbonatemia misdiagnosed as an RTA or as a pseudo-pseudo-RTA because acidemia and RTA are both absent. As demonstrated, pseudo-RTA is determined by blood gas analysis. Sustained hypocapnia, as occurred in this patient, fosters additional adaptive responses, the basis of which can lead to a mimicking of dRTA as detailed in the following clinical vignette.

CLINICAL SUMMARY

- Pseudo-renal tubular acidosis (pseudo-RTA) is a heterogeneous group of disorders characterized by hyperchloremia, hypobicarbonatemia, and metabolic acidosis that is not due to intrinsic renal tubular dysfunction.
- Diagnosis of RTA requires a structured approach in assessing primary and secondary acid-base responses.
- Respiratory alkalosis can present with a picture that is similar to distal RTA; blood gas analysis is mandatory.
- A fundamental appreciation of the limitations and application of urinary indices is required to evaluate metabolic acidosis

PATIENT SCENARIO 2

A 55-year-old female with a history of cerebrovascular injury with residual hemiparesis, alcohol-induced cirrhosis, and hypertension presented with altered mental status. The vital signs were temperature 38.5°C, pulse 110 beats per minute, respiratory rate 18 breaths per minute, and blood pressure 80/58 mm Hg. Hemodynamic parameters improved after administration of intravenous saline. The initial laboratory examination showed the following: Na^+, 128 meq/L; K^+, 3.5 meq/L; Cl^-, 99 meq/L; tCO_2, 19 meq/L; blood urea nitrogen, 22 mg/dL; creatinine, 1.42 mg/dL; and albumin 3 g/dL. Prior laboratory data were not available for comparison. An arterial blood gas analysis, obtained to evaluate altered mental status, showed a pH 7.40, PCO_2 33.3 mmHg, and bicarbonate 20.1 meq/L. The urine dipstick pH was 6.0. Urine chemistries were Na^+ 12 meq/L, K^+ 62 meq/L, and Cl^- 22 meq/L.

In contrast to the first clinical scenario, hyperventilation is not an obvious feature that leads one to immediately suspect respiratory alkalosis. Furthermore, important elements of the history and physical examination may be difficult to ascertain during the initial encounter. In this patient, the systemic pH within the normal range can be explained by either chronic respiratory alkalosis or a mixed disorder (respiratory alkalosis and metabolic acidosis).

When the clinical history supports chronic respiratory alkalosis, determining whether the decrease in bicarbonate is appropriately compensated is critical to complete analysis of the blood gas. Metabolic compensation during chronic respiratory alkalosis was investigated during hypobaric hypoxia by Krapff and associates in their seminal study in humans; a decrease of 10 mm Hg of PCO_2 was paralleled by a decrease in bicarbonate of 0.4 to 0.5 meq/L.[10] Computing the expected serum bicarbonate for a PCO_2 of 33 mmHg in our patient closely approximates the expected compensation, signifying the presence of chronic respiratory alkalosis.

If respiratory alkalosis is not the initial consideration and one presumes metabolic acidosis to be the primary disorder, assessment of urinary ammonium (NH_4^+) handling can be pursued to identify the origin of hyperchloremic acidosis, ie, renal or nonrenal. In many diagnostic algorithms of normal anion gap acidosis, the evaluation of the urine anion gap is recommended as the next step.[1,11] The UAG representing the difference between the principal cations (Na^+ and K^+) and anions (Cl^-) is used to reflect renal ammonium excretion. A negative value denotes excretion of unmeasured cations (UCs) (NH_4^+) with Cl^-. A positive UAG implies decreased urinary NH_4^+ excretion as encountered with dRTA.[12,13] In our patient, the urine pH of 6, positive UAG of 52 meq/L, and K^+ in the low normal range point toward a diagnosis of dRTA. Examining the physiologic response and limitations of the aforementioned diagnostic tests (Table 1) delineates the mechanisms whereby respiratory alkalosis mimics dRTA.

Respiratory Alkalosis and Renal Compensation

Bicarbonaturia may be detected within 2 to 5 hours of the onset of acute respiratory alkalosis.[8,14,15] A net decrease in luminal activity of the Na^+-H^+ exchanger and basolateral Na^+/HCO_3^- exchanger subsequently occurs.[16] Experimental dog studies, later replicated in 8 acutely hyperventilating males, documented that a 10 mm Hg decrease in PCO_2 was accompanied by a serum bicarbonate decrement of 2 meq/L. [1,15] Persistent hypocapnia elicited

Table 1. Clinical Applications and Limitations of the Urine Anion Gap

Urine Anion Gap = $(Na^+ + K^+) - Cl^-$ (meq/L)	
Clinical Application	Interpretation
HCMA: proximal RTA or gastrointestinal losses	UAG < 0 meq/L indicates appropriate renal NH_4^+ excretion.
HCMA: distal RTA	UAG > 0 meq/L indicates reduced NH_4^+ excretion.
Respiratory alkalosis	UAG > 0 meq/L indicates decreased NH_4^+ excretion. Differentiated from HCMA by systemic pH ≥ 7.40.
Limitation	
Excess anions	Unmeasured anions increase urinary Na^+ or K^+ losses with UAG ≥ 0. UOG may distinguish disorder from distal RTA.
Endogenous: ketoacids and lactate	
Anionic drugs and toxins: hippurate, salicylate, and 5-oxoproline	
Dietary: potassium citrate	
Urine pH > 6.5	Indicates urine HCO_3^- excretion and increases UAG, which is corrected by including urine HCO_3^- in UAG calculation.
Urine Na^+ < 25 meq/d	Limited distal Na^+ delivery reduces H^+ secretion; interpretation of UAG may not be valid.
Hyperammonemia	UAG not validated in this condition.
Chronic kidney disease	UAG > 0 from impaired NH_4^+ excretion.
Neonates	UAG should not be used to evaluate renal NH_4^+ excretion during high rates of anion excretion.

Abbreviations: H^+, hydrogen ion; HCMA, hyperchloremic metabolic acidosis; $HCO3^-$, bicarbonate; K^+, potassium; Na^+, sodium; $NH4^+$, ammonium; RTA, renal tubular acidosis; UAG, urine anion gap; UOG, urine osmolal gap.

chronic adaptive measures that transpired over 2 to 3 days (Fig 1).[18]

The urine pH can be noticeably high in the early bicarbonaturic phase of respiratory alkalosis when the systemic pH is alkalemic. However, after 24 hours, bicarbonate excretion gradually decreases. During this phase, a concomitant decrease occurs in urine NH_4^+ excretion, with a net decrease in systemic pH toward 7.40.[18,19] Thus, the primary means of decreasing serum bicarbonate after 24 hours is a limitation of NH_4^+ excretion.[15] Animal models demonstrated that this adaptive process is mediated by reduced activities of the apical H^+-ATPase (vacuolar ATPase) along the entire nephron and of H^+/K^+-ATPase in the collecting tubule, and it is initiated within 6 hours of hypocapnia (Fig 2).[20] As a consequence of these changes in pump activities, there is augmented urinary sodium excretion and chloride reabsorption, resulting in hyperchloremia and subsequent hypobicarbonatemia.[16] During sodium restriction, net kaliuresis is noted, as demonstrated by Gennari and colleagues in dogs.[18] In our patient, the low urine-sodium concentration was attributable to the low distal sodium delivery seen in cirrhosis which stems from a low glomerular filtration rate and enhanced upstream sodium reabsorption.

Mild hypokalemia is frequently encountered in respiratory alkalosis and reflects urinary potassium losses and transcellular shifts.[8] The lower limit of serum bicarbonate in respiratory alkalosis is 7–10 meq/L for acute hypocapnia and 10–12 meq/L for the chronic condition.[8,18,21,22] Interestingly, animal models with low bicarbonate level before induction of hypocapnia also exhibited a further decrease in their bicarbonate level, indicating that the mechanism that regulates the renal response to hypocapnia is independent of the systemic pH.[22]

The urinary indices of chronic respiratory alkalosis and dRTA must be distinguished from one another. In classic dRTA, the first, voided, morning urine pH exceeds 6, signifying an inability to acidify the distal urine. As alluded previously, the initial renal response to the elevated systemic pH is bicarbonaturia. Although there is a gradual decline in urinary bicarbonate losses, the urinary pH does not decline to less than 6. In fact, Gledhill and colleagues demonstrated an increase in urine pH after the initial decline.[15] The urinary pH should be interpreted with caution, however, as insufficient urine sodium concentration, ie, less than 25 meq/L, may produce the illusion of dRTA.[23,24] This classical corollary was described in a patient with diarrhea, in whom the urine pH became less than 5.0 after an initial value greater than 5.5 due to enhanced sodium avidity. Distal sodium delivery was subsequently achieved by a furosemide and sodium sulfate infusion, the sulfate acting as a nonreabsorbable anion in this portion of the nephron. The mechanism purportedly relates to the lack of generation of a transepithelial gradient required for H^+ secretion in the collecting duct. The limited amount of free H^+ in the tubule would result in an elevated pH. Volume depletion, cirrhosis, and congestive heart failure are clinical circumstances that may produce a reversible "functional" dRTA from impaired distal sodium delivery.[24,25]

As surmised from the aforementioned processes, respiratory alkalosis suppresses renal ammonia excretion, maintaining a positive UAG. Consequently, dRTA should be entertained only when UAG is positive in the setting of metabolic acidosis, which is established by either an arterial or arterialized venous blood gas. Caution is advised in the interpretation of UAG in the setting of acute kidney injury and chronic kidney disease as impaired renal

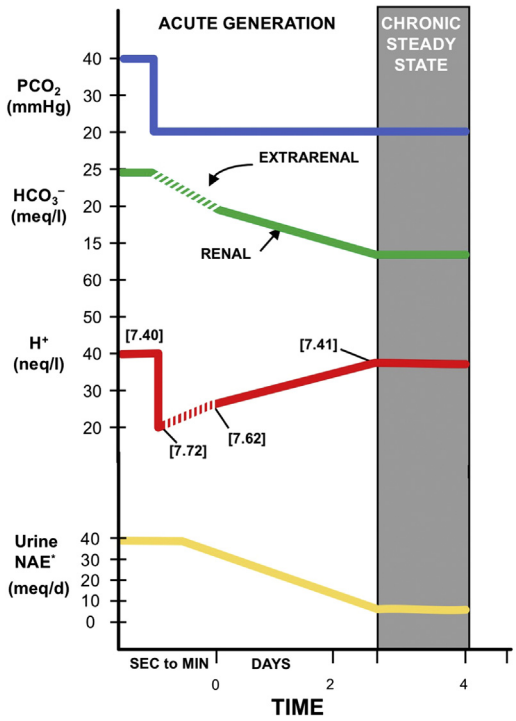

Figure 1. Acid-base parameter changes during sustained hypocapnia. An acute decrease in PCO_2 is accompanied by a rapid elevation in pH (in parenthesis), minimal reduction in serum HCO_3^- concentration, and an abrupt decrease in hydrogen ion concentration (H^+) with pH increase. Extrarenal buffering incompletely restores the pH to normal during the first 1 to 2 days. After 2 to 3 days, renal net acid excretion is maximally depressed, and pH declines to nearly to its normal baseline. Abbreviations: PCO_2, carbon dioxide partial pressure; HCO_3^-, bicarbonate; H^+, hydrogen; NAE, net acid excretion. Values are for illustration only, and they do not reflect actual patient data. Adapted from Reference [17].

acidification is expected in these settings.[26] Furthermore, the test has not been validated in the setting of hyperammonemia. Similarly, cirrhosis or heart failure patients are frequently prescribed renin-angiotensin-aldosterone system inhibitors that may limit renal ammoniagenesis via limitation of aldosterone production or induction of hyperkalemia, both of which may reduce the UAG.[27] The complex nature of this case underscores the importance of using the right tests at the right time.

Overall, the findings of hyperchloremia, hypobicarbonatemia, hypokalemia, and suppressed urine net acid excretion can mimic dRTA.[8] Although the distinction seems obvious, the aforementioned constellation of findings was erroneously reported as RTA in a case series of children with acute neurogenic hyperventilation.[28] In this report of 10 patients with central neurogenic hyperventilation-induced respiratory alkalosis, the authors described the presence of dRTA due to the presence of a positive UAG. Similarly, another report identified bicarbonaturia as a pathological response in a hyperventilatory syndrome.[29] We acknowledge that such misdiagnoses may be not uncommon in daily clinical practice. The rapid evaluation and validation of acid-base status using nomograms based on confidence bands can minimize such clinical pitfalls.[30]

Respiratory alkalosis is among the most common acid-base disorders in the critically ill and can be driven by hypoxemia, pulmonary disease, stimulation of the medullary respiratory center, or from mechanical ventilation.[31] Compared to most etiologies of hypocapnia, liver disease is an underappreciated and misunderstood cause. Increased tidal volume alone can induce hypocapnia. Consequently, tachypnea is not an obligatory feature of respiratory alkalosis. Among chronic, compensated liver disease patients, respiratory alkalosis is evident in 40% of patients and remains the most frequently associated acid-base disturbance.[32] In sharp contrast, cirrhotic patients in the intensive care unit predominantly develop high anion gap and HCMA, highlighting the importance of distinguishing them from respiratory alkalosis.[33] Hyperventilation may arise from diaphragmatic elevation attributable to ascites or hypoxemia-driven increases in minute ventilation as in hepatic hydrothorax or portopulmonary hypertension. The severity of liver disease and associated hyperdynamic status has been shown to correlate with development of respiratory alkalosis, thereby implying the presence of pathogenic byproducts in association with impaired liver metabolism.[34,35] Ammonia has been reported to play a role because of the observed inverse relationship with PCO_2.[36] The limited metabolism of progesterone and estrogen seen in severe liver disease appears the most likely because of hyperventilation. Although serum levels are noticeably lower than those encountered during the gravid state, an impaired blood-brain barrier appears to stimulate the respiratory center.[37]

The importance of distinguishing respiratory alkalosis from hyperchloremic acidosis is best demonstrated in the setting of cirrhosis, as bicarbonate administration is the treatment of choice in hyperchloremic acidosis of renal origin, a therapy that can have deleterious consequences when administered in the setting of respiratory alkalosis. The physiologic effects of respiratory alkalosis in cirrhosis are sparse in the literature, but hypocapnia triggers significant cerebral vasoconstriction, conceivably a protective response to hyperammonemia and other hepatotoxins. Administration of bicarbonate in this setting can increase PCO_2 and induce reflexive cerebral vasodilation. The combined alkalosis can shift the oxygen dissociation curve leftward rendering tissue hypoxia.[14,38] Sodium bicarbonate can potentiate hypokalemia in cirrhosis, a common electrolyte disturbance resulting from the effects of diuretics, lactulose, and respiratory alkalosis. Alkalemia tilts the mass action equation of ammonia-ammonium in favor of the gaseous brain-diffusible state. Hypokalemia provokes hyperammonemia via induction of ammoniagenesis in the proximal tubule, which in concert with worsening alkalemia multiplies the risk for development of cerebral edema.[25,39] Saline loading and hypocalcemia from bicarbonate administration can potentiate cardiotoxic effects of respiratory alkalosis.

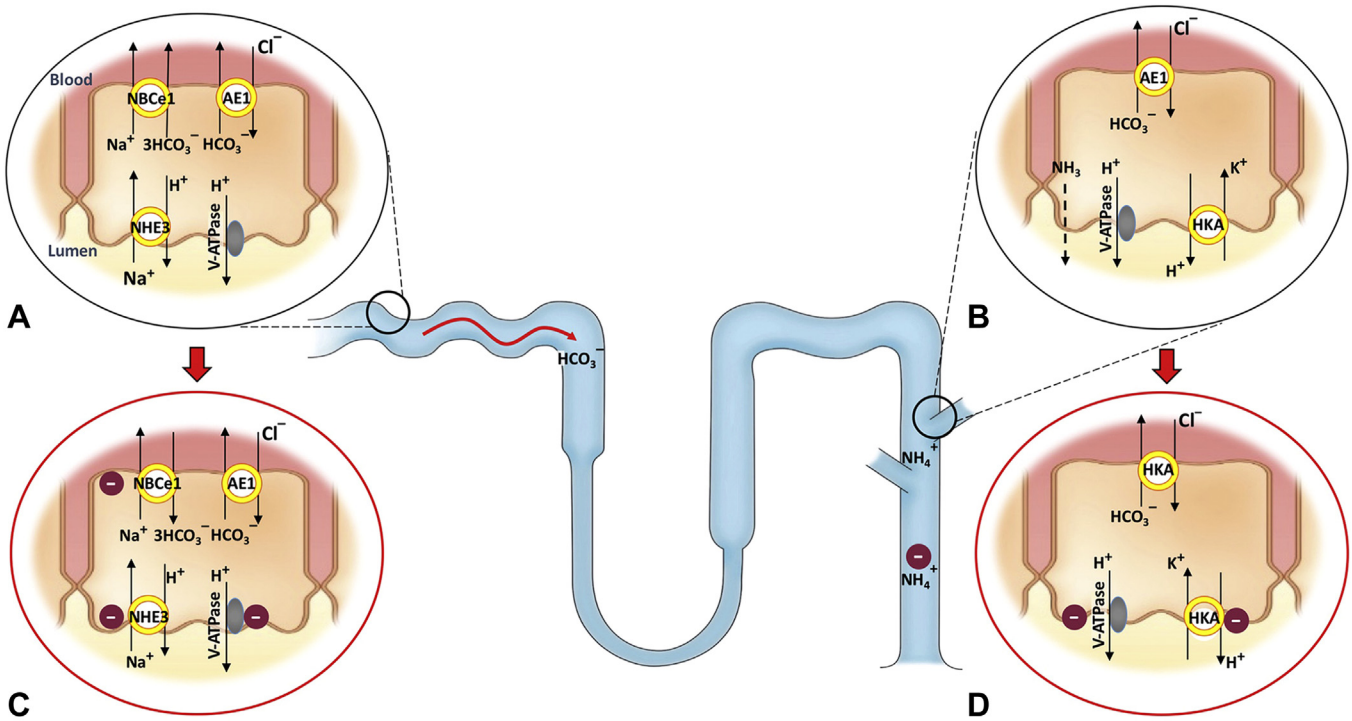

Figure 2. Renal response to chronic respiratory alkalosis. (A) Normal proximal tubule sodium bicarbonate reabsorption: apical sodium (Na^+)/hydrogen (H^+) exchange via the sodium-hydrogen exchanger (NHE3); active H^+ secretion via the vacuolar ATPase (V-ATPase); basolateral sodium bicarbonate (HCO_3^-) reabsorption via the sodium bicarbonate cotransporter (NBCe1); and chloride (Cl^-)/HCO_3^- exchange via anion exchanger-1 (AE1). (B) Normal collecting duct passive ammonia (NH_3) diffusion into the tubular lumen; active H^+ and potassium (K^+) secretion via membrane-bound ion exchanger, H^+/K^+-ATPase (HKA); and Cl^-/HCO_3^- exchange via AE1. (C) and (D) Chronic respiratory alkalosis downregulates (−) activities of NHE3, V-ATPase, NBCe1 in the proximal tubule, and V-ATPase and HKA in the collecting duct. The overall renal compensatory response to sustained hyperventilation is a net decrement of ammonium (NH_4^+) excretion.

PATIENT SCENARIO 3

A 25-year-old non-English speaking, Hispanic male presented with weakness and "wobbliness" of 3 days duration. He reported that he occasionally uses marijuana. His medical, family, and social history were unremarkable. He was afebrile and his heart rate was 87 beats per minute, blood pressure was 105/57 mm Hg, and respiratory rate was 14 breaths per minute. He was lucid and had mild titubation. Otherwise, his examination was unremarkable. Serum chemistries were Na^+ 135 meq/L, K^+ 2.1 meq/L, Cl^- 120 meq/L, tCO_2^- 5 meq/L, blood urea nitrogen 6 mg/dL, and creatinine 0.9 mg/dL. Arterial blood gas results were pH 7.07, PCO_2 14 mmHg, and HCO_3^- 3.8 meq/L. Urinalysis revealed a pH of 6.0, specific gravity of 1.012, and negative tests for glucose and protein. Urine showed Na 37 meq/L, K^+ 38 meq/L, and Cl 70$^-$ meq/L. No additional urine studies were performed.

Gaps in the Urine and Osmolal Gap

The metabolic profile of this hypokalemic patient is reminiscent of dRTA. The PCO_2 of 14 is an appropriate response to acidosis vis-à-vis Winters' equation. The absence of an increased anion gap is evidentiary for a single acid-base disorder, ie, HCMA. The urine pH of 6 and positive UAG may obfuscate the analysis of the specific acid-base disturbance, particularly if more precise tools to estimate urinary ammonium are not available. This patient's acid-base disorder was later determined to have been caused by toluene ingestion once a detailed history was obtained through an interpreter who elicited a history of paint inhalation.

The varying presentations of toluene, a hydrocarbon used as an organic solvent in paints, varnishes, and lacquers, permits us to examine the clinical pearls and perils of urine anion and osmolal gaps. The UAG reflects the difference in measured urine cations and anions. For ease of understanding, the standard equation is rearranged to reflect unmeasured anions (UAs) and UCs, which is UAG = UA – UC. Urinary ammonium (NH_4^+) is the predominant UC.[40] When confronted by an acid load, renal urine NH_4^+ excretion increases, and the UAG becomes more negative.[12] Hepatic oxidation of toluene to benzoic acid and subsequent conjugation to glycine in the mitochondrion forms hippuric acid. Hippuric acid's anion, hippurate, is readily filtered and secreted, thereby adding to the load of urinary UA with reduction of the UAG. Hippurate leaves no footprint as a serum anion. A high-anion-gap metabolic acidosis disappears as a hyperchloremic acidosis appears and because saline is administered to

most toluene insufflators who were evaluated in hospital.[41] Consequently, the sum of known urine cations, Na^+ and K^+, is disproportionately elevated in comparison to Cl^-, with a resultant positive UAG. This relationship is depicted as,

$$Na^+ + K^+ - Cl^- > 0 \text{ and}$$
$$(Na^+ + K^+ + NH_4^+) - (Cl^- + \text{Hippurate}^-) > 0$$

An impression of impaired urinary acidification is rendered because of the positive UAG. The significant hypokalemia seen in this case can be explained by the obligatory loss of urinary cations with the readily excreted hippurate, a nonreabsorbable anion. The hypokalemia, exacerbated by increased aldosterone activity from volume depletion, adds credence to the misdiagnosis of a true RTA in toluene pseudo-RTA. Notably, urine pH may exceed 6 pH units because of enhanced renal ammoniagenesis, ammonium ion acting as a conjugate base and increasing urinary pH. Provided sufficient circulatory volume and maintenance of glomerular filtration, with urinary loss of hippurate, a non-anion gap metabolic acidosis is present. However, as volume depletion ensues from loss of sodium and potassium, a high anion gap is apparent during plasma hippurate retention. Repair of the circulating volume by saline reverts the elevated anion gap to a normal anion gap by displacement of hippurate with chloride; the former is now lost in the urine upon restoration of glomerular filtration. Overzealous reconstitution of the extracellular space with high chloride–containing solutions may produce a dilutional acidosis in right ventricular infarction, ketoacidosis, and large-volume diarrheal states marked by bicarbonate loss.[1] In fact, a normal bicarbonate concentration in an individual presenting with extracellular volume depletion represents an undisclosed metabolic acidosis that is aggravated by chloride administration and converted to HCMA.

The importance of distinguishing toluene pseudo-RTA lies in recognizing that dRTA can indeed be observed in toluene ingestion as demonstrated in a series of 8 patients with toluene-induced acidosis, 2 of whom demonstrated low urinary NH_4^+ excretion.[41] Toluene is thought to impair NH_4^+ secretion in the distal tubule; however, the precise mechanism has not been described to date. In support of distal urine acidification defect, urine PCO_2 was noted to be reduced in an alkaline urine sample among a small group of toluene users. Turtle bladder studies corroborate this finding to be related to impaired H^+ secretion.[42] Chronic interstitial nephritis has also been reported with chronic toluene insufflation, but toluene-induced dRTA is likely to be reversible.

In lieu of the UAG, urinary NH_4^+ can be better estimated via the urine osmolal gap (UOG) and is estimated at approximately half of the UOG.[43]

$$\begin{aligned}\text{UOG} = {} & \text{Measured Urine Osmolality} - 2(U_{Na} + K) \\ & + (\text{Urine Urea Nitrogen(mg/dl)}/2.8) \\ & + (\text{Effective osmole/mol wt})\end{aligned}$$

A UOG of more than 200 milliosmoles/L suggests an appropriate renal response to metabolic acidosis. One caveat is that the UOG may not be reliable in the presence of other osmotically active substances such as mannitol, methanol, or ketones.[44,45] Additional limitations to consider during the assessment of UOG are presented in Table 2.

Diabetes ketoacidosis (DKA) is another RTA mimic. In DKA, several metabolic disorders can develop and overlap. An initial high-anion-gap metabolic acidosis may convert to a non-anion gap acidosis upon loss of urinary keto-anions (after surpassing their renal threshold) during saline administration. Hepatic regeneration of ketone bodies with concomitant sodium bicarbonate infusion may produce a triple metabolic acid-base disturbance of high and normal anion gap metabolic acidosis with metabolic alkalosis.[1] Calculation of the UOG may be helpful in DKA as heightened urinary ammonium excretion is anticipated. Another mimic of RTA is sulfuric acid ingestion. Diagnostic dilemma and difficulty with interpretation of the UAG may be encountered during sulfuric acid ingestion as a folk remedy. Rapid excretion of sulfate anion by means of hippurate may lower an initially increased serum anion gap and lead to the diagnosis of pseudo-RTA.[46]

Validity of laboratory values should also be considered in the investigation of acid-base derangements. During the

Table 2. Clinical Applications and Limitations of Urine Osmolal Gap

Urine Osmolal Gap = Measured Urine Osmolality − 2(U_{Na} + κ) + (U_{Glu}/18) + (UUN/2.8)	
Utility	Interpretation
Assess urine NH_4^+ excretion	Urine NH_4^+ is roughly 0.5 (UOG). Impaired renal acidification when <75 meq/L.
Assess presence of occult anions	When UAG suggests impaired NAE, a UOG > 100 mosmol/kg H_2O may indicate the presence of occult anions (eg, ketoacids, lactate, hippurate, and 5-oxoproline [pyroglutamic acid]).
Limitations	
Urinary tract infection	Urease-producing organisms spuriously increase urine osmolal gap.
Presence of occult anions	False impression that NH_4^+ excretion is high.
Presence of osmotically active agents (mannitol and ethanol)	Failure to account for all osmotically active substances leads to misdiagnosis of enhanced urine NH_4^+ excretion and/or excretion of occult anions.

Abbreviations: Glu, glucose (mg/dL); K, Potassium (meq/L); Na, sodium (meq/L); NH_4^+, ammonium; NAE, net acid excretion; UUN, urea nitrogen (mg/dL); UAG, urine anion gap; UOG, urine osmolal gap (mosmol/kg H_2O).

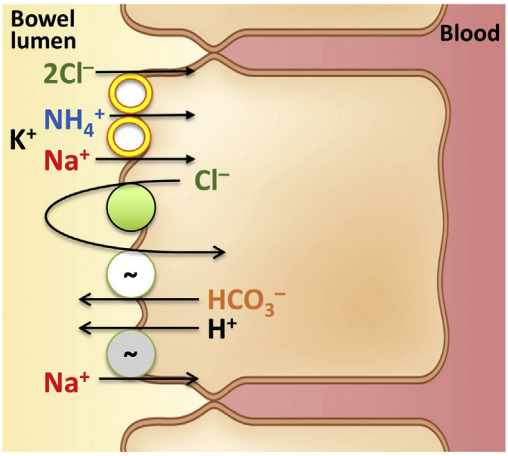

Figure 3. Pathogenesis of hyperchloremic metabolic acidosis in ureteral diversion procedures. Ammonium ions (NH_4^+) replace potassium ions (K^+) and are cotransported from the colonic lumen with sodium (Na^+) and chloride (Cl^-) ions by the sodium-potassium-2 chloride cotransporter. Cl^- is secreted in exchange for bicarbonate (HCO_3^-) via the cystic fibrosis transmembrane conductance regulator (CFTR) and the Na^+-dependent, electroneutral Cl^-/HCO_3^- anion exchanger (AE1).

nonacidemic states, measurement of the UAG will yield a null or slightly positive value owing to endogenous net acid production and excretion. Therefore, judicious interpretation of the serum anion gap is mandatory in the context of metabolic acidosis. Errors in diagnosing RTA may occur when urine net acid excretion is assessed after spuriously low bicarbonate concentrations are reported by diagnostic laboratories in paraproteinemia.[47] Rare clinical circumstances that may produce pseudo-RTAs include bromism and iodism. High levels of bromide or iodide anion may produce low/negative serum anion gaps from "pseudohyperchloremia" because of artifactual measurement as chloride ion.[48] The aforementioned clinical situations underscore the importance of interpreting UAG in the proper context.[49]

Hyperchloremic Acidosis of Urinary Diversion

Sequelae of older modes of urinary diversion surgery represent another pseudo-RTA and include various metabolic derangements inherent to the anatomical techniques used. Urinary diversions are performed after cystectomy, typically for bladder cancer. Native ureters may be implanted into the sigmoid colon (ureterosigmoidostomy) or ileum (ileal conduit). Prolonged urinary residence within sigmoid colonic segments permissively facilitates ionic transport that would be impossible in normal bladder across the colonic epithelium.[50] Colonic luminal anion exchangers secrete bicarbonate into the lumen and reabsorb chloride. Abundant urinary ammonium in the bowel is absorbed via a Na^+-K^+-2-Cl^- cotransporter in lieu of K^+ ion, resulting in resorption of 2 Cl^-, 1 Na^+, and 1 NH_4^+ ions. Cl^- ions are exchanged for HCO_3^- ions leading to HCMA (Fig 3). K^+ ions, replaced by NH_4^+, are excreted and lost in feces, which explains why ureteral diversion procedures produce a nonhyperkalemic form of HCMA.[51,52] Fortunately, The overall consequence of urinary diversion is the development of hyperchloremic acidosis and hypokalemia.[53] Although urine ammonium excretion is intact, by the aforementioned abnormal transport, urinary ammonium would be low if directly assayed. Fortunately, contemporary urinary diversion techniques that employ short, ileal conduits decrease urine dwell times, thereby minimizing the possibility of developing pseudo-RTA.

Cholestyramine, a bile acid sequestrant used rarely for treatment of dyslipidemia, exchanges chloride for bicarbonate. In individuals with normal renal function, this effect is not discernible. When renal function is impaired or with concurrent use of renin-aldosterone system inhibitors, hyperchloremic metabolic acidosis with decreased urine net acid excretion is noted.[52,54]

CONCLUSION

Pseudo-RTA or the misdiagnosis of RTA is not uncommon and may occur when there is clinically unobvious depression of tCO_2 and no blood gas analysis. Because confirmatory tests for RTA such as an ammonium chloride–loading challenge have been stopped from use, clinical diagnosis is limited. A major limitation and diagnostic challenge is the use of surrogate methods of estimating urine net acid excretion, ie, urine ammonium ion concentration. Widespread availability of direct urine ammonium measurement may offset in part the diagnostic confusion imparted by the diagnoses of the pseudo-RTAs.

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