

Differential Diagnosis of Nongap Metabolic Acidosis: Value of a Systematic Approach

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Summary

Nongap metabolic acidosis is a common form of both acute and chronic metabolic acidosis. Because derangements in renal acid-base regulation are a common cause of nongap metabolic acidosis, studies to evaluate renal acidification often serve as the mainstay of differential diagnosis. However, in many cases, information obtained from the history and physical examination, evaluation of the electrolyte pattern (to determine if a nongap acidosis alone or a combined nongap and high anion gap metabolic acidosis is present), and examination of the serum potassium concentration (to characterize the disorder as hyperkalemic or hypokalemic in nature) is sufficient to make a presumptive diagnosis without more sophisticated studies. If this information proves insufficient, indirect estimates or direct measurement of urinary NH_4^+ concentration, measurement of urine pH, and assessment of urinary HCO_3^- excretion can help in establishing the diagnosis. This review summarizes current information concerning the pathophysiology of this electrolyte pattern and the value and limitations of all of the diagnostic studies available. It also provides a systematic and cost-effective approach to the differential diagnosis of nongap metabolic acidosis.

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Introduction

A non-anion gap pattern is commonly found in patients with both acute and chronic metabolic acidosis. Between 19% (1) and 41% (2) of patients in intensive care units with acute metabolic acidosis and 20%–55% of individuals with chronic uremic acidosis have a nongap pattern (3,4). This pattern can originate from a number of pathophysiologic mechanisms; therefore, determination of its cause can be challenging.

In this review, we first describe the mechanisms leading to nongap metabolic acidosis, and then demonstrate that a complete history and physical examination coupled with simple laboratory tests, such as the serum anion gap (and delta gap) and serum potassium concentration, can enable the clinician to determine the cause in a large percentage of cases. When this information is insufficient, studies of renal acidification might be required. The value and limitations of various studies of renal acidification, including urine pH, indirect and direct measures of urine NH_4^+ excretion, and renal bicarbonate reabsorption are explored. The resulting systematic approach to the diagnosis of nongap metabolic acidosis should enable the clinician to determine the cause in a cost-effective and timely manner.

Recognition and Pathogenesis of the Hyperchloremia and Hypobicarbonatemia of Nongap Acidosis

A nongap metabolic acidosis is characterized by a serum anion gap that is unchanged from baseline, or a decrease in serum $[\text{HCO}_3^-]$ that exceeds the rise in

the anion gap (5,6). Whenever possible, the baseline anion gap of the patient should be used rather than the average normal value specific to a particular clinical laboratory (6) and the anion gap should be corrected for the effect of a change in serum albumin concentration (7). These steps will reduce the chance that a co-existing high anion gap acidosis will be missed if the increase in the serum anion gap does not cause the value to exceed the upper limit of the normal range (8,9).

Nongap metabolic acidosis (hyperchloremic) refers a metabolic acidosis in which the fall in serum $[\text{HCO}_3^-]$ is matched by an equivalent increment in serum Cl^- (6,10). The serum anion gap might actually decrease slightly, because the negative charges on albumin are titrated by accumulating protons (6,11). Hyperchloremic acidosis is a descriptive term, and does not imply any primary role of chloride in the pathogenesis of the metabolic acidosis.

As shown in Figure 1, a nongap metabolic acidosis can result from the direct loss of sodium bicarbonate from the gastrointestinal tract or the kidney, addition of hydrochloric acid (HCl) or substances that are metabolized to HCl, impairment of net acid excretion, marked urinary excretion of organic acid anions with replacement with endogenous or administered Cl^- (12,13), or administration of Cl^- -rich solutions during resuscitation (14). The development of hyperchloremic acidosis from administration of HCl is easy to visualize, with titrated HCO_3^- being replaced by Cl^- . Similarly, gastrointestinal or urinary NaHCO_3 loss can lead to a deficit of Na^+ and a reduction in extracellular fluid volume, which stimulates renal retention

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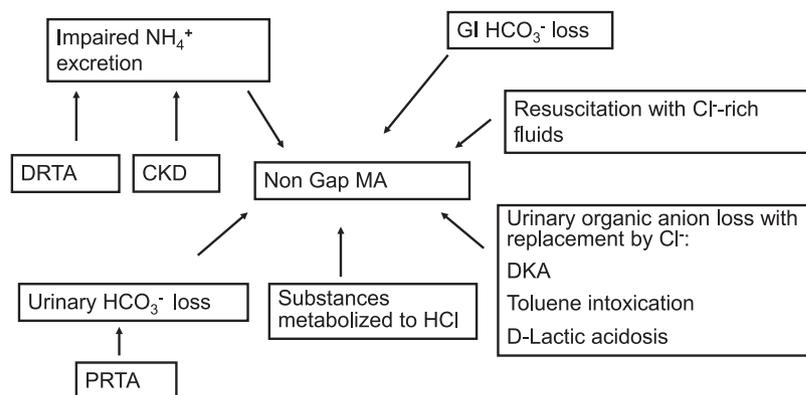


Figure 1. | Potential mechanisms leading to a nongap metabolic acidosis. Several disorders can produce a nongap (hyperchloremic) metabolic acidosis by diverse mechanisms, including loss of bicarbonate in the urine or gastrointestinal tract, failure of bicarbonate generation to match acid production, metabolism of precursors to hydrochloric acid, and administration of chloride-rich solutions. Knowledge of these potential mechanisms can guide the clinician in choosing the studies necessary to obtain the diagnosis while keeping the number of studies to a minimum. GI, gastrointestinal; MA, metabolic acidosis; DRTA, distal RTA; DKA, diabetic ketoacidosis; PRTA, proximal RTA.

of Na^+ and Cl^- , the lost HCO_3^- thereby being replaced by the retained Cl^- .

The nongap metabolic acidosis arising from reduced NH_4^+ excretion is thought to result from a limitation in acid excretion (bicarbonate regeneration) in the presence of a relatively unimpeded excretion of filtered anions (e.g., SO_4^{2-} , $\text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}$) (15). Serum $[\text{HCO}_3^-]$ is first titrated by hydrogen from the acids derived from metabolism resulting in a deficit of HCO_3^- and surfeit of acid anions. In the absence of sufficient NH_4^+ excretion to regenerate the lost HCO_3^- , the anions are excreted with Na^+ and K^+ resulting in a deficit of Na^+ and avid renal retention of filtered Na^+ and Cl^- . Consequently, the retained Cl^- replaces the lost HCO_3^- .

With disorders such as ketoacidosis or toluene intoxication, metabolic acid production is markedly increased. Although NH_4^+ excretion is also strikingly increased, the rate of urinary excretion of the acid anions (ketoanions and hippurate, respectively) exceeds the excretion of NH_4^+ . The anions not excreted with NH_4^+ are excreted with Na^+ and K^+ causing deficits of Na^+ and inducing avid retention of filtered Na^+ and Cl^- , with the lost HCO_3^- being replaced by the retained Cl^- .

Sizable expansion of the extracellular fluid during resuscitation with a solution devoid of HCO_3^- , such as isotonic saline, results in a decrease in serum $[\text{HCO}_3^-]$ and hyperchloremia without a proportional decrease in PCO_2 (dilution acidosis).

Understanding the various mechanisms producing a nongap metabolic acidosis will aid the clinician in determining the most appropriate information needed to identify the cause of the nongap acidosis.

Systematic Approach to Differential Diagnosis

Historical Information and Physical Examination

A complete history and physical examination are very useful in determining the cause. Many cases of acute nongap acidosis are due to infusion of large quantities of Cl^- -rich solutions during resuscitation; therefore, recognition of this entity could prevent further diagnostic studies (14,16).

Cationic amino acids (lysine and arginine hydrochloride) administered in total parenteral solutions are metabolized to HCl (17). HCO_3^- loss from the body via the gastrointestinal tract, as with diarrhea, can cause a nongap acidosis. Both the anion composition and the quantity of the diarrheal fluid are determinants of whether metabolic acidosis ensues (18). Thus, metabolic acidosis is more common with secretory than inflammatory diarrhea, in part because of the higher concentration of HCO_3^- in the diarrheal fluid of the former type (18).

Various medications that inhibit renal bicarbonate reabsorption (e.g., acetazolamide), produce hypoaldosteronism (e.g., PG inhibitors), or impair sodium-dependent proton secretion (e.g., amiloride) can contribute to the development of nongap acidosis. Diversion of the urinary collecting system after removal of the bladder either into the sigmoid or the ileum will commonly result in nongap metabolic acidosis (19).

Genetic disorders that compromise distal or proximal proton secretion can be associated with abnormalities of other organ systems (20). For example, hearing loss is observed with certain forms of distal renal tubular acidosis (RTA), ocular disease is found with some causes of proximal RTA, and osteopetrosis and mental retardation are seen with mixed proximal-distal RTA. The presence of these abnormalities should cause the clinician to consider accompanying disorders of renal acidification.

Because the kidney is central to the regulation of acid-base balance, evidence of renal insufficiency is important. With metabolic acidosis of CKD, a decrease in serum $[\text{HCO}_3^-]$ is usually observed once GFR is $<20\%$ – 25% of normal (15). The serum $[\text{HCO}_3^-]$ is often ≥ 15 mEq/L, and there is a rough correlation between the severity of the CKD and the metabolic acidosis (21,22). Early in the course of CKD, the metabolic acidosis is often nongap in nature (21), although a nongap acidosis can be present even with severe CKD (4).

The presence of hypoaldosteronism or diseases with tubulointerstitial damage, such as sickle cell disease or chronic interstitial nephritis, can reduce renal acid excretion to a

greater extent than observed with typical glomerular disease (15,23,24). Therefore, the acidosis might be more severe than expected or appear at an earlier stage of renal dysfunction and will be characterized by a predominant nongap pattern.

It seems reasonable to attribute the acidosis to CKD alone when the acidosis seems to be consistent with the degree of renal impairment. By contrast, it is worthwhile to consider further evaluation of renal acidification if the metabolic acidosis is present early in the course of CKD (eGFR >30 ml/min per 1.73 m²) or is more severe than expected (serum [HCO₃⁻] <15 mEq/L), is associated with hyperkalemia out of proportion to the level of renal function, and is largely characterized by a normal anion gap.

Laboratory Studies

Acid-Base Parameters. The electrolyte pattern characteristic of nongap acidosis is indistinguishable from that observed with chronic respiratory alkalosis (10). Therefore, it is essential to examine the pH and PaCO₂ to be sure that metabolic acidosis, rather than respiratory alkalosis, is present.

Serum Anion Gap and Delta Anion Gap. Individuals with distal and proximal RTA with normal renal function or those given hydrochloric acid precursors have a pure nongap acidosis. By contrast, those with CKD (with or without hyporeninemic hypoaldosteronism), certain organic acidoses such as ketoacidosis, toluene intoxication, and D-lactic acidosis, or profuse diarrhea (sufficient to produce hyperproteinemia and hypotension-induced lactic acidosis) can have a nongap acidosis, a high anion gap acidosis, or both (12,25–27). Therefore, a combined nongap and high anion gap metabolic acidosis would be evidence against distal or proximal RTA with normal renal function, or less than extreme gastrointestinal bicarbonate loss. Thus, determining whether nongap acidosis alone or a combination of the two forms is present can provide useful information. The serum electrolyte patterns of disorders characterized by a nongap acidosis at some point during their course are shown in Table 1.

Serum Potassium. As shown in Table 2, the disorders producing a nongap metabolic acidosis can be divided into those associated with a high or normal serum potassium concentration and those in which serum potassium is low. In cases in which serum potassium is elevated, there is

often impairment in renal excretion of potassium in addition to the reduction in the renal excretion of acid. Examples include the nongap acidosis of CKD, and that due to hypoaldosteronism or intrinsic damage to the collecting duct. Drugs that inhibit the renin-angiotensin system or block the epithelium-like sodium channel, also impair potassium as well as hydrogen secretion.

With administration of HCl or precursors (28), the serum potassium might be elevated initially because of the pH-dependent efflux of cellular K⁺. However, kaliuresis occurs as the acidosis persists, causing serum potassium to return to baseline or actually fall below normal (29). The enhanced kaliuresis has been attributed to increased distal Na⁺ delivery coupled with increased aldosterone secretion (29–31).

Disorders in which serum potassium is low include those in which potassium is directly lost from the gastrointestinal tract; however, a gastrointestinal mechanism for hypokalemia is also at play with ureterosigmoidostomy or ureteroileostomy, even though the excreted potassium actually appears in the urine.

Kaliuresis producing hypokalemia is prominent with distal or proximal RTA. The magnitude of the hypokalemia with distal RTA parallels the severity of the acidosis and is related in part to the associated enhanced aldosterone secretion (31). Correction of the acidosis often attenuates the potassium wasting, although base replacement fails to correct the potassium wasting in some cases, suggesting an intrinsic defect in tubular potassium handling (31).

With proximal RTA, the hypokalemia is most severe when bicarbonaturia is prominent, as is observed during the generation of the metabolic acidosis or during its treatment with base (31,32).

Assessment of Renal Acidification

If the history and physical examination along with simple laboratory studies do not enable the clinician to determine the cause of the metabolic acidosis, assessment of renal acidification is indicated (25,26,33).

Assessment of Net Acid Excretion. An increase in the body’s acid load causes a rise in net acid excretion (primarily in the form of urinary NH₄⁺). Urinary NH₄⁺ can increase from a baseline value of approximately 20 to 40 mEq/d with a normal endogenous acid load to >200 mEq/d with large acid loads (34). Failure to excrete

Table 1. Typical electrolyte pattern in various acid-base disorders characterized by nongap acidosis

Parameter	Normal	Distal RTA	Proximal RTA	CKD ^a		Toluene Intoxication ^a		Ketoacidosis ^a	
				Early	Late	Early	Late	Early	Late
Na ⁺ (mEq/L)	140	140	140	140	140	140	140	135	135
K ⁺ (mEq/L)	4.0	3.5	3.5	4.4	4.6	3.5	3.3	3.6	3.3
Cl ⁻ (mEq/L)	105	110	110	110	110	105	120	100	110
HCO ₃ ⁻ (mEq/L)	25	20	20	20	15	10	10	10	10
Anion gap (mEq/L)	10	10	10	10	15	25	10	25	15

^aAn electrolyte pattern consistent with nongap acidosis, mixed nongap and high anion gap, or high anion gap alone can be present at any time during the course of this disorder.

Table 2. Causes of nongap metabolic acidosis categorized based on serum K⁺

High or Normal Serum K ⁺	Low Serum K ⁺
Administration of HCl TPN solutions NH ₄ Cl ^b Hyperkalemic distal RTA hyporeninemic hypoaldosteronism tubular resistance to aldosterone aldosterone deficiency Chronic renal failure Gordon's syndrome Decreased distal Na delivery Administration of Cl ⁻ -rich solutions ^b Drugs such as triamterene, amiloride, pentamidine, NSAIDs, CEIs, ARBs, trimethoprim, spironolactone, or heparin	Diarrhea Intestinal fistulae Proximal RTA Distal RTA Ureteroileostomy Ureterosigmoidostomy Toluene intoxication Ketoacidosis ^b D-Lactic acidosis Administration of Cl-rich solutions ^b
TPN, total parenteral nutrition; NSAIDs, nonsteroidal anti-inflammatory drugs; CEIs, converting enzyme inhibitors; ARBs, angiotensin receptor blockers.	
^a Includes the majority, but not all, causes of nongap metabolic acidosis.	
^b Serum K ⁺ can be high, normal, or low, depending on when it is determined during the course of the disorder.	

appropriate quantities of urinary NH₄⁺ can produce a nongap metabolic acidosis. Therefore, assessment of urinary NH₄⁺ excretion can be a valuable step in the evaluation of patients with a nongap metabolic acidosis (34,35).

As indicated in Table 3, individuals in whom the acidosis is due only to a defect in distal acidification will have urine NH₄⁺ excretion <20–40 mEq/d. On the other hand, the excretion of <200 mEq/d of NH₄⁺ at 3–5 days after an acidifying stimulus will reflect at least a partial defect in renal acidification.

Indirect Estimates of Urinary NH₄⁺ Excretion

Because direct measurements of urinary NH₄⁺ excretion are not available in most clinical laboratories, investigators have made use of the effect of changes in urinary NH₄⁺ and its accompanying anions on urinary charge (urine anion gap) or osmolality (urine osmolal

gap) to indirectly estimate urinary NH₄⁺ concentration (25,36–39).

Urine Anion Gap. The total charge of the positive ionic species appearing in the urine, including Na⁺ + K⁺ + Ca²⁺ + Mg²⁺ + NH₄⁺, is equal to the total charge of the negative ionic species in the urine, including Cl⁻ + organic anions (OA⁻) + HCO₃⁻ + SO₄²⁻ + H₂PO₄⁻/HPO₄²⁻. Under most circumstances, any increment in urine NH₄⁺ is accompanied by an increment in urine Cl⁻. Assuming that the urinary concentrations of the cations and anions other than Na⁺, K⁺, and Cl⁻ and NH₄⁺ do not change appreciably with an acid load (an assumption that is not completely correct), the urinary NH₄⁺ concentration can be estimated by subtracting the Cl⁻ concentration from the sum of the concentrations of Na⁺ + K⁺ (36,37), using a calculation termed the urine anion gap, which is as follows:

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

In studies examining the relationship between urine NH₄⁺ concentration and the urine anion gap, a linear relationship was detected (37), with the urine anion gap becoming more negative as urinary NH₄⁺ excretion rose. The following mathematical formula was derived from these studies: NH₄⁺ = -0.8 (urine anion gap) + 82, which allowed for an estimate of urinary NH₄⁺ excretion (37). In general, the urine anion gap averaged -20 to -50 mEq/L in individuals who retained the ability to excrete adequate quantities of NH₄⁺ (36,37). By contrast, it was less negative or even positive in individuals in whom urinary NH₄⁺ excretion was low (36).

There are limitations to the use of the urine anion gap. When anions other than Cl⁻, such as β-hydroxybutyrate or acetoacetate in ketoacidosis or hippurate in toluene intoxication, are excreted in the company of NH₄⁺ (13,25,26), the value for NH₄⁺ derived using the urine anion gap will significantly underestimate the actual urinary NH₄⁺ excretion (25).

An additional situation in which the urine anion gap (or other measures of renal acidification) might not reflect

Table 3. NH₄⁺ excretion under various conditions

Condition	NH ₄ ⁺ Excretion (mEq/d)
Normal	20–40
Normal with acid loading	200 ^a
Patients with distal RTA	<20–40
Patients with proximal RTA ^b	<20–40
Patients with acidifying state and defect in net acid excretion ^b	<200

^aMaximal renal NH₄⁺ excretion will be reached by 3–5 days and could be less than this if values are obtained after <3–5 days.

^bAny value less than maximal value obtained after 3–5 days will reflect a defect in net acid excretion. Although controversial, some studies indicate that urine net acid excretion can be below the level expected for the acidemic state in patients with proximal RTA both during its genesis (when bicarbonate in the urine is ample) and during the steady state (when bicarbonate is absent from the urine).

the intrinsic ability of the kidney to excrete net acid is when distal Na^+ delivery (and subsequent Na^+ reabsorption) is impaired (as is observed with a Na^+ -avid state detected by urine $\text{Na}^+ < 25$ mEq/L) (40). The reduced distal Na^+ reabsorption decreases the lumen negative electrical gradient that favors hydrogen secretion and thus causes a functional distal RTA characterized by reduced NH_4^+ excretion and an elevated urine pH. This state can be reversed by augmenting distal Na^+ delivery either by volume expansion or other methods of increasing distal Na^+ delivery such as administration of sodium sulfate.

Urine Osmolal Gap. To overcome some of the limitations of the urine anion gap, the urine osmolal gap was developed (25,41,42). The osmolality of the urine is the result of the presence of the charged cations and their accompanying anions, as well as that of the neutral substances, including creatinine, urea, and glucose. The NH_4^+ concentration therefore can be estimated by subtracting the contributions to the osmolality of all of these substances except NH_4^+ from the measured osmolality, a calculation termed the urine osmolal gap (25,41). Because it was assumed that the concentrations of Mg^{2+} , Ca^{2+} , $\text{H}_2\text{PO}_4^-/\text{HPO}_4^-$, and creatinine would not change appreciably with an acid load, these values were omitted from the formula. Furthermore, to simplify the calculation, the contribution of the anions accompanying Na^+ and K^+ were accounted for by multiplying the concentrations of the cations by 2: –

$$\begin{aligned} \text{Urine Osmolal Gap} = & \text{Measured Urine Osmolality} - 2 \\ & \times [\text{Na}^+ + \text{K}^+] \\ & + \text{Urea Nitrogen (mg/dl)}/2.8 \\ & + \text{Glucose (mg/dl)}/18. \end{aligned}$$

This method of estimating urinary NH_4^+ concentration enabled the clinician to assess changes in NH_4^+ concentration irrespective of the accompanying anion (13,25,26). It is therefore useful in the evaluation of all causes of nongap metabolic acidosis (25,26,38,43).

Studies examining the relationship between urine NH_4^+ concentration estimated from the urine osmolal gap and the actual urine NH_4^+ concentration in individuals with and without metabolic acidosis revealed a strong positive linear correlation, the urine osmolal gap increasing as urine NH_4^+ excretion rose (38,41).

A simple modification of this formula, in which the value obtained was divided by 2 to reflect the contribution of the anions accompanying NH_4^+ to the osmolality, termed the modified urine osmolal gap, resulted in values close to the measured urine NH_4^+ (38,39,41):

$$\begin{aligned} \text{Modified Urine Osmolal Gap} = & \\ & \left[\text{Measured Urine Osmolality} - 2 \times [\text{Na}^+ + \text{K}^+] \right. \\ & \left. + \text{Urea Nitrogen (mg/dl)}/2.8 + \text{Glucose (mg/dl)}/18 \right] / 2 \end{aligned}$$

The value for NH_4^+ obtained can also be expressed per gram of creatinine or per millimole of creatinine excreted to obtain an estimate of daily excretion. When expressed in the latter fashion, a normal ratio is >3 . Although this method represented an improvement over the urine anion

gap, potential inaccuracies were recognized if there was enhanced excretion of unusual uncharged compounds (such as alcohols), polyvalent anions, or cations (such as Ca^{2+} and Mg^{2+}).

The modified urine osmolal gap is not capable of detecting small changes in urine NH_4^+ excretion. Indeed, comparison of values of urine NH_4^+ estimated using this formula with values measured directly in healthy controls without an exogenous acid load (39) revealed that estimated values could be as much as 43.2 mmol/L below or 34.4 mmol/L above those measured directly.

Therefore, as concluded when the concept was first proposed, this method is most valuable at the bedside to screen for gross changes in urine NH_4^+ concentration to differentiate between patients with appropriate increments in urine NH_4^+ concentration and those in whom urine NH_4^+ excretion is compromised (25,44).

Direct Measurement of Urinary NH_4^+ . To date, NH_4^+ has not routinely been measured directly because the traditional methods utilized for this purpose, such as the formaldehyde titration method, are labor intensive and expensive (45). However, the enzymatic assay used in many clinical laboratories for measuring serum NH_4^+ can be easily modified by predilution of the urine by 1:100 or greater, thereby enabling this determination to be accomplished using an autoanalyzer (45,46). Studies comparing the accuracy of this method with the formaldehyde titration method show good agreement (45,46), and reveal that the determination can be completed within 30 minutes. The estimated cost of each determination is approximately \$5–6 USD (46). Further study of the usefulness and cost-effectiveness of this method seems warranted.

Urine pH. Normal individuals subject to acute acid loading have a urine pH <5.5 and often <5.3 , whereas individuals with impaired acidification, such as those with hypokalemic distal RTA (type 1), have a urine pH >5.5 (47,48). Although urine pH is reduced to <5.5 in normal individuals in response to an acute acid load (minutes to hours), with more prolonged metabolic acidosis (more than a few days) urine pH can increase to >5.5 , even in the presence of ample quantities of NH_4^+ (36,49). This rise in urine pH has been attributed to buffering of H^+ by the increased NH_3 produced by the kidney. Thus, a urine pH >5.5 will not necessarily be associated with a low NH_4^+ excretion.

Even if urine pH is appropriately low (*i.e.*, <5.5), urine NH_4^+ excretion can be compromised as observed, for example, with hypoadosteronism (type IV RTA) (36). The low NH_4^+ excretion in this disorder has been attributed in part to suppression of ammonia synthesis by hyperkalemia because lowering serum potassium concentration can reverse the defect (50).

Although urine pH considered in isolation is not adequate to assess renal acidification, once urinary NH_4^+ excretion has been established as low, measurement of urine pH can be helpful in distinguishing among disorders in which the ability to generate a maximal hydrogen gradient is compromised (type I distal RTA, hyperkalemic distal RTA characterized by tubular damage) and those in which it is unaltered (such as hypoadosteronism). In all instances, urine should be collected under mineral oil to prevent

dissipation of CO₂ and a falsely elevated urine pH. Figure 2 shows typical urine pHs with various disorders causing nongap acidosis.

Other Measures of Distal Urinary Acidification

Studies to further elucidate the nature of the renal acidification defect have been developed and could be of interest (51). Two of the most frequently utilized measures are described below.

Urine-Blood PCO₂ Test. NaHCO₃ is infused intravenously at a rate to maintain serum [HCO₃⁻] at 25–26 mEq/L and urine pH at approximately 7.5, and the urine-blood pCO₂ difference is calculated (52). A value ≥30 mmHg (often close to 70 mmHg) is found in normal individuals and a value <30 mmHg is found in those with impaired distal hydrogen secretion. Using these criteria, the test was shown to have a high specificity and sensitivity for detecting defects in distal proton secretion (52). However, cases have been reported in which the urine-blood PCO₂ is low, but NH₄⁺ excretion is appropriately increased (35). Therefore the test should be done only after NH₄⁺ excretion has been determined.

Furosemide Administration. Administration of furosemide shifts sodium distally augmenting distal hydrogen secretion. Prior salt depletion or co-administration of mineralocorticoid during the test was shown to increase the sensitivity of the test. Practically, after a baseline urine sample, 40–80 mg of furosemide and 1 mg of fludrocortisone are given; samples of urine are collected for 3–4 hours and urine pH is evaluated. Normal individuals lower urine pH <5.3, whereas those with defective hydrogen secretion fail to lower urine pH <6.0 (51).

Additional Studies

Additional studies might be helpful in differential diagnosis of disorders with impaired net acid excretion. Measurements of plasma aldosterone and renin will confirm the diagnosis of aldosterone deficiency, with or without

hyporeninemia. Measurement of urinary citrate can be helpful in distinguishing between individuals with distal forms of RTA and those with proximal RTA. It will be low in the former and often elevated in the latter disorder.

Renal Bicarbonate Reabsorption

In disorders in which the function of the proximal tubule is compromised (proximal RTA), there is a decrease in the renal HCO₃⁻ threshold, normally 22 mEq/L in infants and 25–26 mEq/L in children and adults (53). The threshold can be variable in individuals with proximal RTA but usually is >15 mEq/L. Bicarbonate appears in the urine when serum [HCO₃⁻] is above the threshold, whereas bicarbonate disappears from the urine when it is below this value. In the latter stage, the urine pH will be <5.5 although urine NH₄⁺ excretion has been found to be low (54). Therefore, this disorder can have some characteristics of low aldosterone states. However, proximal RTA will be easily recognized by the requirements for large quantities of base to raise serum [HCO₃⁻], the appearance of bicarbonaturia at a normal serum [HCO₃⁻] concentration, and the presence of hypokalemia.

Proximal RTA can be confirmed by demonstrating that fractional HCO₃⁻ excretion is >15%–20% when serum [HCO₃⁻] is raised to normal values by infusion of NaHCO₃:

$$FE_{HCO_3} \% = \frac{\text{Urine } HCO_3^- \times \text{Serum Creatinine}}{\text{Serum } [HCO_3^-] \times \text{Urine Creatinine}} \times 100$$

Although bicarbonate reabsorption can be affected alone, defects are more commonly present in the function of other proximal tubule transporters such as sodium-dependent glucose and phosphate transporters and amino acid and uric acid transporters. If so, glucose, phosphate, uric acid, and amino acids will appear in the urine in increased amounts often leading to a reduction in their serum concentrations. Therefore, in patients suspected of having

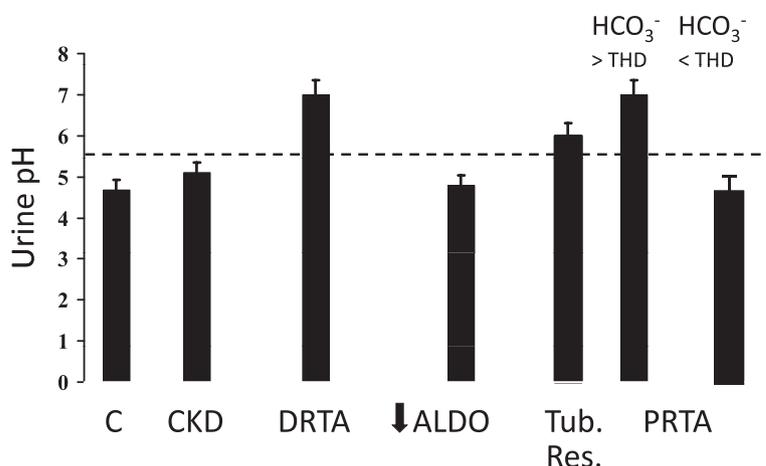


Figure 2. | Urine pH in different disorders. Acidification of the urine in controls after an acute acid load results in a urine pH <5.5 (dotted line). Similarly, urine pH will be <5.5 in patients with CKD, those with low aldosterone states, and PRTA when the serum [HCO₃⁻] is below the reabsorptive threshold. By contrast, it will be >5.5 in patients with DRTA, those with tubular resistance to aldosterone, and those with PRTA when the serum [HCO₃⁻] is above the reabsorptive threshold. THD, reabsorptive threshold; C, controls; DRTA, distal RTA; aldo, aldosterone; tub. res, tubular resistance; PRTA, proximal RTA.

proximal RTA, measurement of serum glucose, uric acid, and phosphate is indicated. Table 4 summarizes the studies commonly utilized in the evaluation of nongap metabolic acidosis.

A nongap metabolic acidosis is increasingly recognized in patients with acute or chronic metabolic acidosis. Defects in renal regulation of acid-base balance can cause this electrolyte pattern. This pattern is also present in individuals

Table 4. Common studies utilized in the evaluation of nongap metabolic acidosis

Study	Purpose	Value	Limitations
Anion gap	Detection of nongap acidosis and presence of co-existing high anion gap acidosis	Critical to classification of patients as having nongap acidosis; important to detect co-existing high anion gap acidosis	Wide variability of normal among individuals can cause miscategorization; several disorders can have combined nongap and high anion gap acidosis
Serum K ⁺	Classifying disorder as having high/normal or low serum K ⁺	Certain disorders are characterized by elevated or normal serum K ⁺ , whereas others are characterized by low serum K ⁺ . Therefore, examination of serum K ⁺ provides helpful information in differential diagnosis	Some disorders can fit in both categories, so distinction between disorders is not absolute
Urine anion gap	Indirect estimate of urine NH ₄ ⁺ excretion	Estimate of main component of renal acid excretion. Abnormal value suggests that the kidney contributes to the development of the nongap acidosis	Only a qualitative estimate of urine NH ₄ ⁺ excretion. Underestimates urine NH ₄ ⁺ excretion in presence of increased excretion of anions other than chloride
Urine osmolal gap	Indirect estimate of urine NH ₄ ⁺ excretion	Estimate of main component of renal acid excretion. Low urine NH ₄ ⁺ excretion suggests that the kidney contributes to the development of the nongap acidosis. Most accurate indirect estimate. Low cost and ease of performance	Not as accurate at low values of urine NH ₄ ⁺ or in presence of increased concentration of alcohols
Urine pH	Assessment of kidney ability to acidify urine and theoretically excrete net acid	Simple to perform	Inappropriately elevated pH can be present with chronic acidosis in absence of impaired acidification. Appropriately reduced pH can be present with impaired net acid excretion

Table 5. Systematic approach to diagnosis of nongap metabolic acidosis

<p>Obtain a good history and physical examination to determine if acidosis is acute or chronic in nature and to look for evidence of disorders associated with nongap acidosis</p> <p>Examine the patient's baseline anion gap corrected for serum albumin to determine if nongap acidosis or combined nongap and high anion gap acidosis is present</p> <p>Examine serum potassium concentration to determine if it is elevated/normal or low</p> <p>Examine eGFR to determine if renal insufficiency is present, which could be associated with nongap acidosis</p> <p>If this information is insufficient to make a diagnosis, obtain measures of renal acidification</p> <p>Measure urine osmolality Na⁺, K⁺, urea nitrogen, and glucose, if glycosuria present, to calculate urine osmolal gap</p> <p>If urine NH₄⁺ assay is readily available, determine urine NH₄⁺</p> <p>Once urine NH₄⁺ is determined to be low, measure urine pH</p> <p>If proximal RTA is suspected, evaluate renal bicarbonate reabsorption</p> <p>If proximal RTA is suspected, evaluate urine for glucosuria, aminoaciduria, and phosphaturia. Check serum for levels of these substances</p>

in whom abnormalities of renal acidification are not the primary cause; therefore, determination of the cause can be obtained without sophisticated studies of renal acidification. A systematic and cost-effective approach to diagnosing nongap metabolic acidosis is detailed in Table 5 that integrates information from the history, physical examination, simple laboratory studies, and sophisticated studies of renal acidification, when necessary.

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Disclosures

None.

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