

# Use of Urine Electrolytes and Urine Osmolality in the Clinical Diagnosis of Fluid, Electrolytes, and Acid-Base Disorders



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We discuss the use of urine electrolytes and urine osmolality in the clinical diagnosis of patients with fluid, electrolytes, and acid-base disorders, emphasizing their physiological basis, their utility, and the caveats and limitations in their use. While our focus is on information obtained from measurements in the urine, clinical diagnosis in these patients must integrate information obtained from the history, the physical examination, and other laboratory data.

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**KEYWORDS:** hyperkalemia; hypokalemia; hyponatremia; polyuria; renal tubular acidosis; urine electrolytes; urine osmolality

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We discuss the use of urine electrolytes and urine osmolality ( $U_{Osm}$ ) in the clinical diagnosis of some disorders of fluid, electrolytes, and acid-base balance.<sup>1–3</sup> Whereas there are usual ranges for the rates of excretion of water and electrolytes and the  $U_{Osm}$ , there are no “normal” values. Data should be interpreted in the context of the expected renal response for the clinical situation. For example, a rate of potassium ( $K^+$ ) excretion of 60 mmol/d is within the usual range for  $K^+$  excretion in adults but indicates renal  $K^+$  wasting in a patient with hypokalemia and a defect in renal  $K^+$  excretion in a patient with hyperkalemia.

## Patients With Potassium Disorders

In response to a low dietary  $K^+$  intake, the rate of  $K^+$  excretion in normal individuals fell to 10 to 15 mmol/d.<sup>4,5</sup> The rate of  $K^+$  excretion rose to match  $K^+$  intake in normal individuals given a large  $K^+$  load (>200 mmol/d) on a long-term basis, with only a modest rise in the plasma  $K^+$  concentration ( $P_K$ ).<sup>6,7</sup>

The urine tests that have been commonly used to assess the renal response to hypokalemia or hyperkalemia are the calculation of the transtubular  $K^+$  concentration gradient (TTKG) and the ratio of the

concentration of  $K^+$  and the concentration of creatinine in a spot urine sample ( $U_K/U_{Creatinine}$ ).

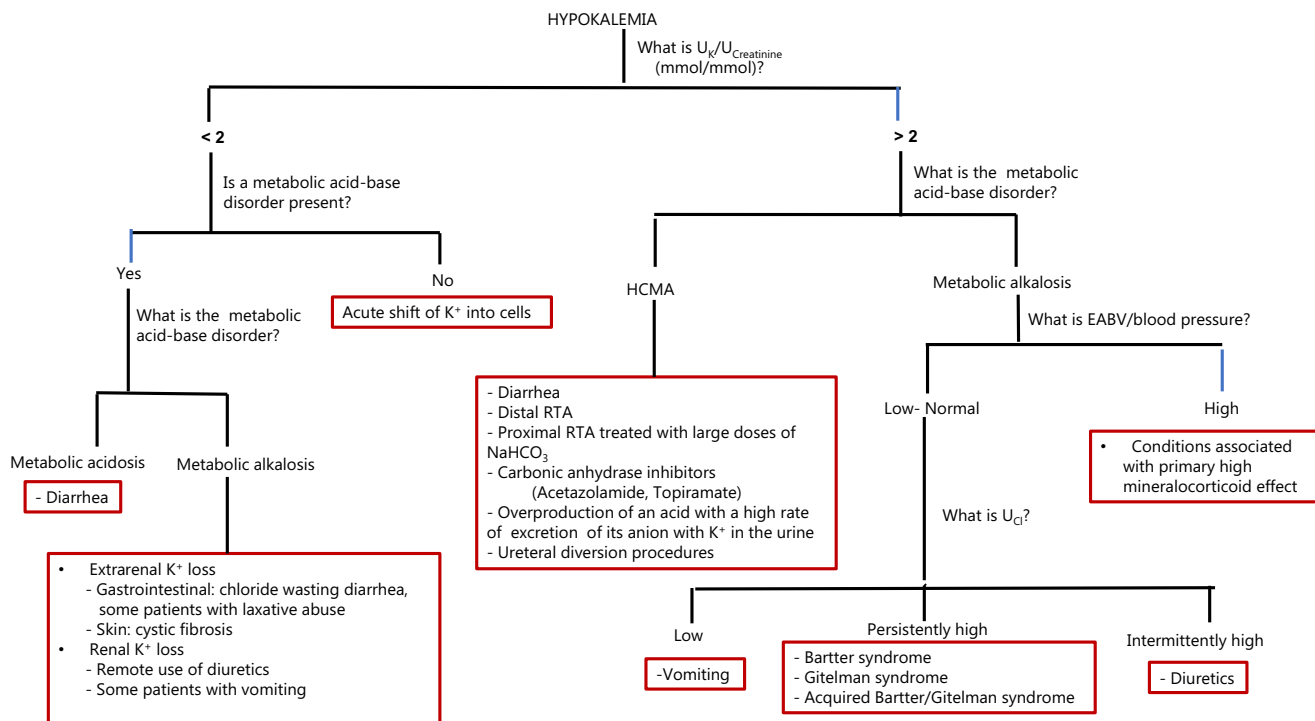
## The TTKG

The TTKG was proposed as a semiquantitative index of the driving force for  $K^+$  secretion in the aldosterone-sensitive distal nephron (ASDN), which includes the second part of the distal convoluted tubule, the connecting segment, and the cortical collecting duct (CCD).<sup>8,9</sup> The TTKG is the ratio of the  $K^+$  concentration in the luminal fluid at the end of the CCD ( $K_{CCD}$ ), and the  $P_K$ . To estimate  $K_{CCD}$ ,  $U_K$  is adjusted for water reabsorption in the medullary collecting duct (MCD), by dividing  $U_K$  by the ratio of  $U_{Osm}$  to plasma osmolality ( $P_{Osm}$ ), because the osmolality of the fluid at the end of the CCD should be equal to  $P_{Osm}$  when arginine vasopressin (AVP) acts.

The assumption in this calculation is that there is no appreciable reabsorption of osmoles in the MCD. Although this is largely correct for electrolytes, it is not for urea because of the process of intrarenal urea recycling.<sup>10,11</sup> Extrapolating from micropuncture studies in rats, we estimate that in adult individuals consuming a typical Western diet, ~600 mmol of urea per day is reabsorbed in the inner MCD and recycled back to the distal convoluted tubule.<sup>12,13</sup> This adds 2 l/d to the volume of fluid at the end of the CCD (600 osm divided by an osmolality of 300 mosm/kg water [ $H_2O$ ]), which constitutes ~40% of this volume (~5 l/d).<sup>13</sup> Not accounting for urea recycling considerably overestimates  $K_{CCD}$  because it considerably underestimates the flow rate in the terminal

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**Figure 1.** Urine data in the clinical approach to the patients with hypokalemia. A urine potassium ( $U_K$ )/urine creatinine ( $U_{Creatinine}$ )  $<2$  and the absence of a metabolic acid-base disorder suggest that the major cause of hypokalemia is an acute intracellular shift of  $K^+$ . The  $U_K/U_{Creatinine}$  may be  $<2$  in some patients with renal  $K^+$  loss (e.g., some patients with vomiting) and  $>2$  in some patients with extrarenal  $K^+$  loss (some patients with diarrhea). The causes for renal  $K^+$  loss can be differentiated by the associated metabolic-acid base disorder. In patients with metabolic alkalosis, further differential diagnosis is based on assessment of the effective arterial blood volume (EABV) and the blood pressure. In the group with low/normal EABV and blood pressure, measurement of chloride concentration in the urine ( $U_{Cl}$ ) provides useful clues to determine the cause of the renal  $K^+$  loss. Conditions associated with primary increased mineralocorticoid effect include primary hyperreninemic hyperaldosteronism (e.g., renal artery stenosis, renin-secreting tumor), primary hyperaldosteronism (e.g., adrenal adenoma, bilateral adrenal hyperplasia, glucocorticoid-remediable hyperaldosteronism), conditions in which cortisol acts as a mineralocorticoid (e.g., apparent mineralocorticoid excess syndrome, ingestion of compounds containing glycyrrhizic acid which inhibits  $11\beta$  hydroxysteroid dehydrogenase-2, adrenocorticotropic hormone-producing tumor), and constitutively active epithelial sodium channel (e.g., Liddle syndrome). RTA, renal tubular acidosis; HCMA, hyperchloremic metabolic acidosis;  $NaHCO_3$ , sodium bicarbonate.

CCD. This error cannot be adjusted for because a number of factors affect the process of urea recycling, including protein intake, hormones (AVP, angiotensin II, aldosterone), cytotoxins, drugs (e.g., cyclosporine), medullary interstitial disease, and chronic renal dysfunction.<sup>14–21</sup>

Because of this error, we do not use the TTKG in the clinical assessment of the patients with dyskalemias.<sup>13,22</sup>

### $U_K/U_{Creatinine}$

Because creatinine is excreted at a nearly constant rate throughout the day, one can use the  $U_K/U_{Creatinine}$  to assess the rate of  $K^+$  excretion.<sup>13,23–26</sup> A caveat in this calculation, as in any calculation that uses the ratio of the concentration of a substance to the concentration of creatinine in a spot urine sample to estimate a 24-hour excretion rate, is that the rate of creatinine excretion, which depends on muscle mass, may be appreciably different in the patient from the usual rate of creatinine excretion ( $\sim 10$  mmol/d [ $\sim 1$  g/d]).

### Patients With Hypokalemia

Hypokalemia could be due to the acute shift of  $K^+$  into cells or chronic loss of  $K^+$  via a renal or extrarenal route.

The expected  $U_K/U_{Creatinine}$  in patients with hypokalemia due to an intracellular shift of  $K^+$  is  $<2$  mmol  $K^+$ /mmol creatinine ( $<18$  mmol  $K^+$ /g creatinine).<sup>23,24</sup> These low values, however, may be also observed in patients with hypokalemia due to extrarenal  $K^+$  loss (e.g., patients with diarrhea or laxative abuse) and in some patients with hypokalemia due to renal  $K^+$  loss (e.g., remote use of diuretics, some patients with chronic vomiting). These patients can be differentiated from those with hypokalemia due to an intracellular shift of  $K^+$  by the presence of a metabolic acid-base disorder. Patients with hypokalemia due to large-volume diarrhea frequently have hyperchloremic metabolic acidosis (HCMA), and patients with hypokalemia due to vomiting or the use of diuretics frequently have metabolic alkalosis (Figure 1). Patients

with hypokalemia due to laxative abuse, however, commonly have no significant metabolic acid-base disorder or only a small increase in plasma bicarbonate ( $\text{HCO}_3^-$ ) concentration.<sup>27</sup>

In patients with chronic hypokalemia, the first step is to examine the acid-base status in plasma.<sup>23,28–32</sup> Patients with metabolic acidosis commonly have HCMA (Figure 1). Notwithstanding, although the hypokalemia in patients with diarrhea is largely due to the loss of  $\text{K}^+$  in diarrhea fluid, the  $U_{\text{K}}/U_{\text{Creatinine}}$  may be high if renal excretion of  $\text{K}^+$  is stimulated because of aldosterone released in response to low effective arterial blood volume (EABV), associated magnesium depletion and the effect of acidemia to decrease the reabsorption of  $\text{Na}^+$  and  $\text{Cl}^-$  in the proximal convoluted tubule (PCT), the increased delivery of  $\text{Na}^+$  and  $\text{Cl}^-$  to the ASDN may result in a higher rate of  $\text{K}^+$  excretion because of increased rate of electrogenic reabsorption of  $\text{Na}^+$  and increased flow rate in the ASDN.<sup>33,34</sup>

In patients with chronic hypokalemia and metabolic alkalosis,  $U_{\text{K}}/U_{\text{Creatinine}} < 2$  mmol  $\text{K}^+$ /mmol creatinine suggests extrarenal  $\text{K}^+$  loss; for example, in sweat (patients with cystic fibrosis) or via the intestinal tract (patients with congenital or acquired chloride wasting diarrhea due to decreased activity of the colonic down-regulated in adenoma anion exchanger). Hypokalemia in patients with vomiting is largely due to renal loss of  $\text{K}^+$  because of stimulation of  $\text{K}^+$  secretion in the ASDN by increased delivery of sodium bicarbonate ( $\text{NaHCO}_3$ )<sup>35–37</sup>; the  $U_{\text{K}}/U_{\text{Creatinine}}$  may be low in these patients in the absence of increased distal delivery of  $\text{NaHCO}_3$ .

Patients with metabolic alkalosis and  $U_{\text{K}}/U_{\text{Creatinine}}$  higher than stated above have renal  $\text{K}^+$  loss. The primary pathophysiology is an increased number of open epithelial Na channels in the luminal membrane of principal cells in the ASDN leading to a higher rate of electrogenic  $\text{Na}^+$  reabsorption.<sup>25,38</sup> This could be due to two groups of disorders. Patients in the first group have low EABV causing the release of aldosterone. Patients in the second group have conditions associated with a primary high mineralocorticoid effect.

The use of chloride concentration in the urine ( $U_{\text{Cl}}$ ) in the differential diagnosis in patients in the first group is shown in Figure 1. The diuretic effect in some patients may be due to an inherited disorder affecting NaCl reabsorption in the medullary thick ascending limb of the loop of Henle (i.e., Bartter syndrome) or the distal convoluted tubule (i.e., Gitelman syndrome).<sup>39,40</sup> A clinical picture that mimics Bartter syndrome may result from activation of the calcium-sensing receptor in the medullary thick ascending limb of the loop of Henle by calcium in patients with hypercalcemia or by other cationic ligands (e.g., gentamicin, amikacin, cisplatin, and possibly cationic immunoglobulins).<sup>41–44</sup>

Acquired Gitelman syndrome has been reported in some patients with autoimmune diseases.<sup>44–46</sup>

Measurement of  $U_{\text{Cl}}$  in multiple urine samples may help in differentiating patients with Bartter syndrome or Gitelman syndrome (persistently high  $U_{\text{Cl}}$ ) from those with diuretic abuse (intermittently high  $U_{\text{Cl}}$ ). An assay for diuretics in the urine, if required, should be performed in urine samples with high  $U_{\text{Cl}}$ . Hypocalciuria ( $U_{\text{Calcium}}/U_{\text{Creatinine}} < 0.2$  mmol/mmol) is usually present in patients with Gitelman syndrome.<sup>47,48</sup>

### Patients With Hyperkalemia

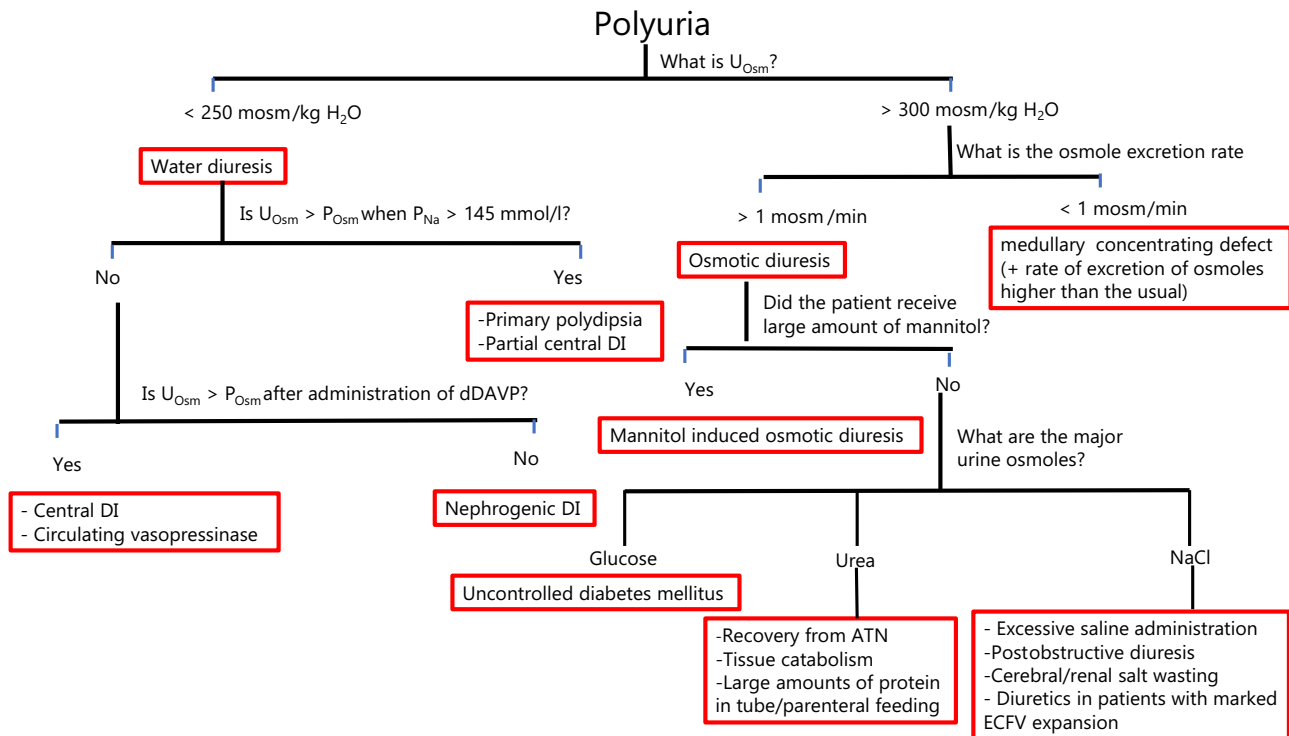
Hyperkalemia caused by a shift of  $\text{K}^+$  out of cells is usually recognized by its acute onset and the clinical setting (e.g., rhabdomyolysis, tumor lysis syndrome, immediate postoperative period, diabetic ketoacidosis, hypoxic lactic acidosis). In a case report of hyperkalemia due to toad venom ingestion (contains bufadienolides, which akin to digitalis, inhibit the  $\text{Na}^+/\text{K}^+$  adenosine 5'-triphosphatase), the  $U_{\text{K}}/U_{\text{Creatinine}}$  was 15.9, indicating that hyperkalemia was not due to a defect in renal  $\text{K}^+$  excretion.<sup>49</sup>

The  $U_{\text{K}}/U_{\text{Creatinine}}$  is less useful in patients with chronic hyperkalemia. This is because to develop chronic hyperkalemia, there must be defect in the renal  $\text{K}^+$  excretion. Hence, the value of assessing  $\text{K}^+$  excretion rate in these patients is to determine whether a large dietary  $\text{K}^+$  intake is contributing to the degree of hyperkalemia. Because of the diurnal variation in  $\text{K}^+$  excretion, this requires a 24-hour urine collection.

A subgroup of patients with chronic hyperkalemia have disorders that cause a decreased number of open epithelial Na channels in the ASDN, leading to decreased rate of electrogenic  $\text{Na}^+$  reabsorption. This includes patients with primary hypoaldosteronism (e.g., Addison disease), patients with pseudohypoaldosteronism type I (e.g., due to molecular defects involving the aldosterone receptor or the epithelial Na channel), and a small subset of patients with hyporeninemic hypoaldosteronism who may have damage to the juxtaglomerular apparatus or a defect in converting prorenin to active renin.<sup>50</sup> Patients with these disorders tend to have renal salt wasting, low EABV, and inappropriately high  $U_{\text{Na}}$  and  $U_{\text{Cl}}$ . Of note, most patients with hyporeninemic hypoaldosteronism, who may also have hyperkalemia, have a clinical picture that mimics the syndrome of hypertension with hyperkalemia (Gordon syndrome or pseudohypoaldosteronism type II).<sup>51</sup> The EABV is not low in these patients, and they do not have renal salt wasting.

### PATIENTS WITH POLYURIA

Polyuria is commonly defined by a urine volume that is  $> 3$  l/d in adults.



**Figure 2.** Urine data in the clinical diagnosis of patients with polyuria. The first step is to determine whether the basis of polyuria is a water diuresis or an osmotic diuresis. A urine osmolality ( $U_{Osm}$ )  $< 250 \text{ mosm/kg H}_2\text{O}$  suggests a water diuresis. This could be due to diabetes insipidus (DI) or primary polydipsia. The cause of the water diuresis can be determined by examining the change in  $U_{Osm}$  in response to a rise in plasma sodium concentration ( $P_{Na}$ ) to  $> 145 \text{ mmol/l}$  and the administration of 1-desamino-8-D-arginine vasopressin (dDAVP). A  $U_{Osm} > 300 \text{ mosm/kg H}_2\text{O}$  suggests that the polyuria is due to an osmotic diuresis or a medullary interstitial disease impairing the process of concentrating the urine in the renal medulla. These 2 disorders can be separated by calculating the rate of excretion of osmoles. The cause of the osmotic diuresis can be determined by measuring the individual osmoles in the urine (e.g., glucose, urea, and sodium chloride [NaCl]). A large amount of mannitol is not commonly given; hence, it is not likely to be the sole cause of a large and sustained osmotic diuresis. ATN, acute tubular necrosis; ECFV, extracellular fluid volume.

In patients suspected of having polyuria, a 24-hour urine collection should be obtained to measure urine volume,  $U_{Osm}$ , creatinine,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ , urea, and glucose and calculate the rate of excretion of osmoles.

A  $U_{Osm} < 250 \text{ mosm/kg H}_2\text{O}$  suggests a water diuresis. The absolute value of the  $U_{Osm}$  depends on the rate of excretion of osmoles.<sup>52</sup> A  $U_{Osm} > 300 \text{ mosm/kg H}_2\text{O}$  suggests an osmotic diuresis and/or a medullary interstitial disease impairing the process of concentrating the urine in the renal medulla.

### Polyuria Due to a Water Diuresis

A water diuresis could be due to primary polydipsia or diabetes insipidus (DI).<sup>53,54</sup> DI may be caused by:

- (i) Central DI: due to lesions affecting the neurohypophysis resulting in deficient synthesis and/or release of AVP. A subset of these patients retain the ability to release AVP in the presence of a higher  $P_{Na}$ , hence described as partial central DI.<sup>55</sup>
- (ii) Nephrogenic DI: due to lesions that interfere with the binding of AVP to its V2 receptor (AVPR2), its effect is to cause trafficking and insertion of aquaporin water channel 2 (AQP2) in the luminal

membrane of principal cells or a defect involving AQP2. Nephrogenic DI may be congenital due to mutations involving the genes encoding for AVPR2 or AQP2 or acquired (most commonly due to intake of lithium).

We prefer not to include patients with a medullary concentrating defect due to a medullary interstitial disease under the category of nephrogenic DI, but rather to characterize them as a separate group. This is because the pathophysiology of the polyuria in these patients is different, their  $U_{Osm}$  is usually  $> 300 \text{ mosm/kg H}_2\text{O}$  (because  $U_{Osm}$  should be at least equal to the osmolality at the end of the CCD (i.e.,  $\sim P_{Osm}$ ), and from a management perspective, decreasing intake of osmoles is more likely to result in a lower urine volume in this group of patients.

- (iii) The presence of a circulating vasopressinase that breaks down AVP. This is commonly caused by its excess release from a large placenta (usually twin or multiple pregnancies) or its impaired degradation by the liver in patients with preeclampsia/HELLP (Hemolysis, Elevated Liver Enzymes, Lowered Platelets) syndrome.

**Table 1.** Electrolyte free water balance versus tonicity balance<sup>a</sup>

Patient	Output		Input		EFW balance	Tonicity balance	
	H <sub>2</sub> O L	Na <sup>+</sup> + K <sup>+</sup> mmol	H <sub>2</sub> O L	Na <sup>+</sup> + K <sup>+</sup> mmol		H <sub>2</sub> O L	Na <sup>+</sup> + K <sup>+</sup> mmol
1	3	150	3	450	-2 L	0	+300
2	3	150	4	600	-2 L	+1	+450
3	3	150	0	0	-2 L	-3	-150

EFW, electrolyte free water.

<sup>a</sup>Three case examples are described. In each patient, the plasma sodium (P<sub>Na</sub>) concentration rose from 140 mmol/L to 147 mmol/L. In all 3 examples, the urine volume was 3 L with a concentration of (Na<sup>+</sup> + K<sup>+</sup>) of 50 mmol/L. Patient 1 received 3 L of isotonic saline (Na<sup>+</sup> concentration 154 mmol/l), patient 2 received 4 L of isotonic saline, and patient 3 received no i.v. fluids. Calculation of the EFW balance shows that the basis of the rise in P<sub>Na</sub> is a negative balance of 2 L of EFW. Calculation of tonicity balance reveals that although the basis of the rise in P<sub>Na</sub> is a net negative balance of 2 L of EFW, this was the result of rather quite different balances for water and (Na<sup>+</sup> + K<sup>+</sup>) in each of the 3 patients. Patient 1 has a positive balance of 300 mmol of Na<sup>+</sup>, patient 2 has a positive balance of 1 L of H<sub>2</sub>O and a positive balance of 450 mmol of Na<sup>+</sup>, and patient 3 has a deficit of 3 L of H<sub>2</sub>O and a deficit of 150 mmol of Na<sup>+</sup>. Hence, the design of the appropriate therapy to correct the hypernatremia and to return the volume and composition of the extracellular and intracellular fluid compartments to their normal values is different for each of them. It requires creating a negative balance for Na<sup>+</sup> in patient 1, a negative balance for H<sub>2</sub>O and Na<sup>+</sup> in patient 2, and a positive balance for H<sub>2</sub>O and Na<sup>+</sup> in patient 3.

Because of difficulties with the measurement of AVP due to its instability in drawn blood samples and inaccuracy of commercially available assays, and because measurements of copeptin are not widely available, clinicians rely on measurement of the change in U<sub>Osm</sub> in response to a sufficient osmotic stimulus (a rise in P<sub>Na</sub> to >145 mmol/L with water deprivation) and after the administration of 1-desamino-8-D-AVP (dDAVP) to determine the cause of a water diuresis.<sup>56,57</sup>

Chronic polyuria decreases the ability to concentrate the urine because of medullary washout.<sup>58-60</sup> A larger volume of water is reabsorbed in the MCD during water diuresis than during antidiuresis.<sup>61,62</sup> The resultant increase in flow in the ascending vasa recta impairs the efficiency of the countercurrent exchange between the ascending and the descending vasa recta and the surrounding medullary interstitium.<sup>63,64</sup> Therefore, if there is a renal response to the release of AVP or the administration of dDAVP, the rise in U<sub>Osm</sub> may vary depending on the degree of this medullary washout but is expected to be at least to a value exceeding the osmolality at the end of the CCD (~P<sub>Osm</sub>).

A rise in U<sub>Osm</sub> to a value that is >P<sub>Osm</sub> in response to a rise in P<sub>Na</sub> >145 mmol/l suggests that the cause of the water diuresis is primary polydipsia or partial central DI.<sup>65-67</sup>

dDAVP is administered if this response to a rise in P<sub>Na</sub> >145 mmol/l is not observed. A rise in U<sub>Osm</sub> to >P<sub>Osm</sub> in response to the administration of dDAVP suggests that the cause of the water diuresis is complete central DI. Notwithstanding, although the U<sub>Osm</sub> of 3 of the 7 patients who were thought to have central DI in the study by Zerbe and Robertson<sup>65</sup> more than doubled after the administration of AVP, it did not rise to a value >P<sub>Osm</sub>.<sup>65</sup> This could be interpreted to suggest

downregulation of AQP2 during water diuresis. Of note however, U<sub>Osm</sub> was measured at 30 and 60 minutes after the administration of AVP; hence, mixing of urines with low and higher osmolality (especially if there is incomplete bladder emptying) may be suspected.

A rise in U<sub>Osm</sub> to a value > P<sub>Osm</sub> after the administration of dDAVP is also expected in patients with water diuresis caused by breakdown of AVP by a circulating vasopressinase, because dDAVP is not degraded by these enzymes. These patients are expected not to respond to the administration of AVP. This investigation should not be attempted in pregnant women, because AVP has an oxytocic effect, unlike dDAVP which has been safely administered during pregnancy.<sup>68</sup>

If the U<sub>Osm</sub> fails to rise appropriately in response to a rise in P<sub>Na</sub> >145 mmol/L and the administration of dDAVP, the diagnosis is nephrogenic DI (Figure 2).

### Polyuria Due to an Osmotic Diuresis

A U<sub>Osm</sub> >300 mosm/kg H<sub>2</sub>O suggests that the polyuria is caused by an osmotic diuresis and/or a low medullary interstitial osmolality due to a medullary interstitial disease. These 2 disorders can be differentiated by calculating the rate of excretion of osmoles in a timed urine collection (multiply the urine flow rate by the U<sub>Osm</sub>). The usual rate of excretion of osmoles in adults consuming a typical Western diet is ~0.5 mosm/min. In patients with osmotic diuresis, the osmole excretion rate is usually >1 mosm/min. Conversely, if the osmole excretion rate is appreciably less than that, a medullary concentrating defect with a higher than usual rate of excretion of osmoles (e.g., in a patient who consumes a diet high in salt and animal protein) may be suspected.

An osmotic diuresis may be due to organic (mannitol, urea, or glucose) or NaCl osmoles, or a combination of these osmoles (Figure 2).

In patients with urea-induced osmotic diuresis, it is important to determine whether the source of urea is exogenous from the intake of proteins or endogenous from catabolism of tissue proteins. Because close to 16% of the weight of protein is nitrogen, 16 g of nitrogen will be produced when 100 g of protein is oxidized. The molecular mass of nitrogen is 14, and each molecule of urea contain 2 atoms of nitrogen; therefore, ~570 mmol of urea is produced from the oxidation of 100 g of protein.

### Patients With Acute Dysnatremia

Calculations of electrolyte free water (EFW) balance and tonicity balance are used to determine the basis for an acute change in P<sub>Na</sub> and the therapy needed to return the P<sub>Na</sub> to a normal value. These calculations can only

**Table 2.** Urine Na<sup>+</sup> and urine Cl<sup>-</sup> concentrations in patients with decreased effective arterial blood volume<sup>a</sup>

Condition	Urine Na <sup>+</sup>	Urine Cl <sup>-</sup>
Vomiting		
Recent	High	Low
Remote	Low	Low
Diuretics		
Recent	High	High
Remote	Low	Low
Diarrhea/some patients with laxative abuse	Low	High
Barter syndrome/Gitelman syndrome/Barter-like syndrome	High	High
Cerebral/renal salt wasting	High	High
Some patients with hyporeninemic hypoaldosteronism	High	High
Adrenal insufficiency	High	High

<sup>a</sup>High: urine concentration of Na<sup>+</sup> or Cl<sup>-</sup> >15 mmol/l; low: urine concentration of Na<sup>+</sup> or Cl<sup>-</sup> <15 mmol/L. Urine Cl<sup>-</sup> may be high in patients with laxative abuse if they have a high rate of excretion of NH<sub>4</sub><sup>+</sup> because of metabolic acidemia or because of hypokalemia, the latter is associated with a fall in pH in proximal convoluted tubule cells and increased production of NH<sub>4</sub><sup>+</sup>. The U<sub>Na</sub> and U<sub>Cl</sub> may not be high in patients with disorders associated with renal loss of Na<sup>+</sup> and Cl<sup>-</sup>, if there is marked degree of decreased effective arterial blood volume as mechanisms to enhance Na<sup>+</sup> and Cl<sup>-</sup> reabsorption in nephron segments other than those affected by the disorder are activated.

be done in a hospital setting, where inputs and outputs are recorded and the concentrations of electrolytes in the urine are measured.

The difference between these 2 calculations is illustrated with case examples of 3 patients, in each of whom P<sub>Na</sub> rose from 140 mmol/l to 147 mmol/l (Table 1). Each patient excreted 3 L of urine with (U<sub>Na</sub> + U<sub>K</sub>) of 50 mmol/l, patient 1 received 3 L of isotonic saline (Na<sup>+</sup> concentration 154 mmol/l), patient 2 received 4 L of isotonic saline, and patient 3 received no i.v. fluids. Total body water in each patient was 40 L.

### EFW Balance

Because urea is not an effective osmole in the body, calculation of EFW balance rather than osmole free water balance was suggested to determine the basis of a dysnatremia and its impact on cell volume.<sup>69</sup> This calculation is based on determining how much water needs to be added to (or subtracted from) a solution to make its tonicity equal to the normal plasma tonicity. In the absence of hyperglycemia, tonicity of plasma water is approximated by the concentrations of (Na<sup>+</sup> + K<sup>+</sup>) × 2 to account for accompanying anions (i.e., ~300 mosm/kg plasma water, with a concentration of Na<sup>+</sup> in plasma water ~150 mmol/l). To calculate EFW balance, one needs to know the volumes and the concentrations of (Na<sup>+</sup> + K<sup>+</sup>) of the input and the urine over the time period the P<sub>Na</sub> has changed.

Applying the calculation of EFW to patient 1, there is no EFW in the input because it has the same tonicity as plasma water. With regard to the output, this patient excreted the equivalent of 1 L of an isotonic solution and 2 L of EFW. Hence, this patient has a negative EFW balance of 2 L. Because total body water is down by

5% (2/40 L), the P<sub>Na</sub> rises by 5% to 147 mmol/l, and hence the administration of 2 L of EFW is required to return the P<sub>Na</sub> back to 140 mmol/l. Applying the EFW balance calculation to the other 2 patients gives the same result, a negative EFW balance of 2 L, and suggests that the appropriate therapy for each of them is the administration of 2 L of EFW.

### Tonicity Balance

A tonicity balance refers to the balance of both water and of (Na<sup>+</sup> + K<sup>+</sup>).<sup>70-72</sup> To calculate a tonicity balance, one needs to know the volumes and the quantity of (Na<sup>+</sup> + K<sup>+</sup>) of the input and the urine over the time period the P<sub>Na</sub> has changed.

Calculation of tonicity balance reveals that while it is true that the basis for the rise in P<sub>Na</sub> in all 3 patients is a net negative balance of 2 L of EFW, this is the result of rather quite different balances for water and for (Na<sup>+</sup> + K<sup>+</sup>) in each of them (Table 1). Hence, the design of the appropriate therapy to return P<sub>Na</sub> to its normal value and restore the normal volume and composition of the ECF and ICF compartments is different for each one of them.

### Patients With Low EABV

In response to decreased EABV, mechanisms that lead to retention of Na<sup>+</sup> and Cl<sup>-</sup> by the kidney are activated. Because 24-hour urine collections to measure the excretion rates of Na<sup>+</sup> and Cl<sup>-</sup> are not practical in clinical settings, U<sub>Na</sub> and U<sub>Cl</sub> values of <15 mmol/l in spot urine samples are used instead to suggest decreased EABV. These are concentration terms that are also affected by the urine flow rate. The 24-hour excretion rate can be estimated by multiplying the ratio of U<sub>Na</sub> or U<sub>Cl</sub>/U<sub>Creatinine</sub> by an estimate of the 24-hour creatinine excretion based on the patient's muscle mass.

There are some caveats in using U<sub>Na</sub> and U<sub>Cl</sub> to detect low EABV (Table 2).<sup>30,73</sup> A low rate of excretion of Na<sup>+</sup> and Cl<sup>-</sup> may reflect a low intake of NaCl rather than a low EABV. The U<sub>Na</sub> might not be low despite low EABV if the excretion of the cation Na<sup>+</sup> is obligated by the excretion of an anion other than Cl<sup>-</sup> (e.g., HCO<sub>3</sub><sup>-</sup> in a patient with recent vomiting [bicarbonaturia is suggested by the finding of an alkaline urine pH], anions of drugs such as piperacillin or carbenicillin). The U<sub>Cl</sub> may not be low despite low EABV if the excretion of the anion Cl<sup>-</sup> is obligated by the excretion of another cation (e.g., NH<sub>4</sub><sup>+</sup> in patients with diarrhea, lithium in patients with lithium intoxication). Both U<sub>Na</sub> and U<sub>Cl</sub> may not be low despite low EABV in patients with diuretic use/abuse, patients with Bartter syndrome or Gitelman syndrome, patients with adrenal insufficiency, patients with cerebral/renal salt wasting, and in a subset of patients with hyporeninemic hypoaldosteronism.

## Patients With Hyponatremia

The clinical approach to the patients with hyponatremia centers on determining the cause of the release of AVP despite hypotonicity. In one group of patients, AVP release is due to decreased EABV. In contrast, in the group of patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or the syndrome of inappropriate antidiuresis to include patients with mutations in AVPR2 causing it to be constitutively active, the release of AVP is not caused by low EABV.<sup>74,75</sup> Notwithstanding, the degree of decreased EABV in some of the patients who are considered in the first group (e.g., some patients with thiazide-induced hyponatremia, patients with “tea and toast” hyponatremia) does not seem to be large enough to cause the release of AVP.<sup>76–79</sup> Reduced EFW excretion in these patients may be caused by a decreased volume of filtrate delivered to the distal nephron as a result of increased reabsorption in the PCT in response to a mild degree of EABV contraction, particularly in elderly patients with reduced glomerular filtration rate, and the presence of other mechanisms for water reabsorption in the distal nephron that are independent of AVP actions.<sup>79–82</sup>

A mild degree of EABV contraction cannot be reliably detected by physical examination.<sup>83,84</sup> Laboratory tests that are based on the expected renal response to decreased EABV are suggested to help separate patients with decreased EABV from those with SIADH.<sup>85,86</sup> The diagnostic accuracy of these tests is limited, particularly in elderly patients who more commonly have hyponatremia

A  $U_{Na} > 30$  mmol/l and fractional excretion (FE) of  $Na^+$  ( $FE_{Na}$ ; Equation 1)  $> 0.5\%$  are thought to be in keeping with euolemia and the diagnosis of SIADH. The  $U_{Na}$  may be  $< 30$  mmol/l, however, in some patients with SIADH if their salt intake is low, and  $> 30$  mmol/l in elderly patients who may have decreased ability to conserve salt despite decreased EABV and in the steady state excrete the salt they eat.<sup>87,88</sup> The calculation of the  $FE_{Na}$  is also affected by the glomerular filtration rate (e.g., for the same rate of  $Na^+$  excretion,  $FE_{Na}$  will be twice as high in an individual whose glomerular filtration rate is reduced by 50% compared with another individual who has a normal glomerular filtration rate). A  $U_{Na} > 30$  mmol/l was observed in 30% of the patients with hyponatremia who were thought to have hypovolemia,  $FE_{Na}$  was  $< 0.5\%$  in 40% of patients who were thought to have SIADH.

$$FE_{Na} = [U_{Na} / P_{Na}] \times [P_{Creatinine} / U_{Creatinine}] \times 100 \quad (1)$$

Reabsorption of urea and urate in the PCT is increased in response to decreased EABV. FE of urea ( $FE_{Urea}$ )  $< 50\%$  was observed in 80% of patients who

were thought to have hypovolemia, but also in 50% of patients who were thought to have SIADH. FE of urate ( $FE_{Urate}$ )  $< 10\%$  was observed in only 60% of patients who were thought to have hypovolemia and also in 35% of patients who were thought to have SIADH.

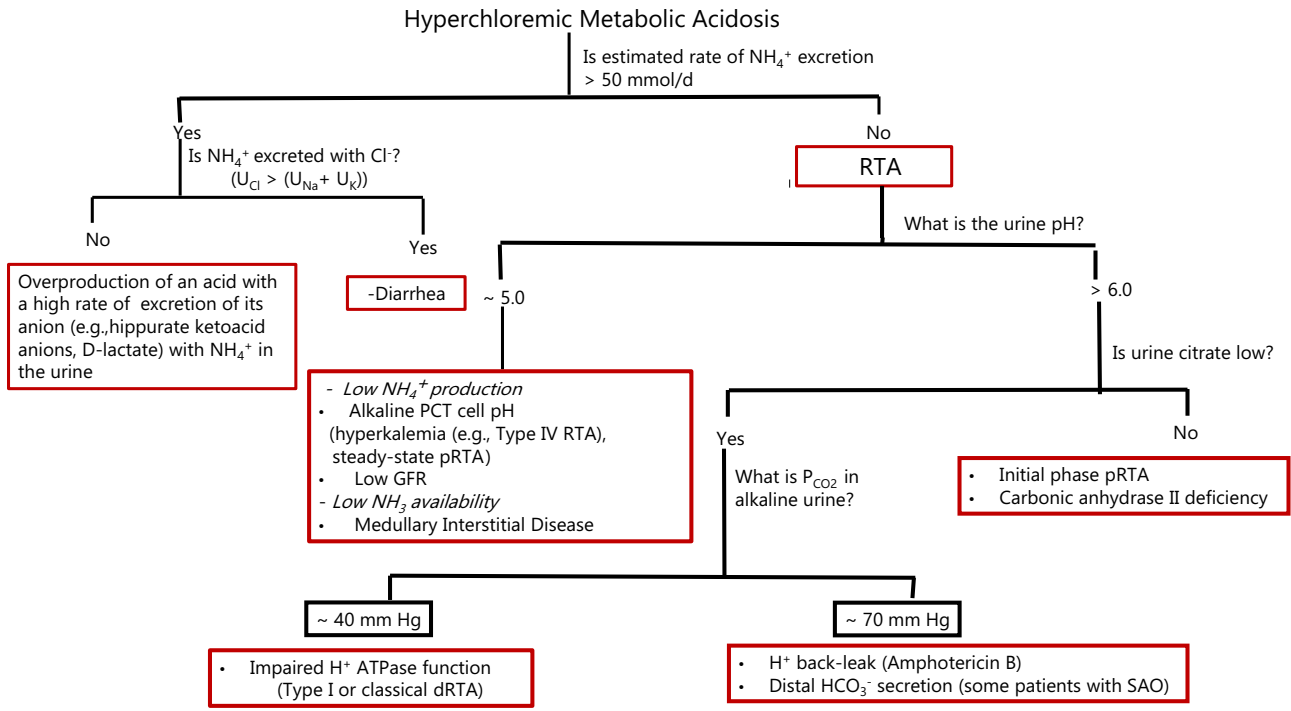
A trial of EABV expansion with infusion of saline may be required to differentiate patients with SIADH from those with mildly contracted EABV. The occurrence of water diuresis is expected in patients with low EABV but not in patients with SIADH, who are also expected to rapidly excrete the salt load. Of note, a subset of patients ( $\sim 20\%$ ) with SIADH may have diminished baroreceptors sensitivity, mimicking the effect of decreased EABV. EABV expansion in this subset of patients may activate these stretch baroreceptors, leading to inhibition of the release of AVP and the excretion of a dilute urine.<sup>89</sup>

With discontinuation of thiazides and provision of salt, patients with thiazide-induced hyponatremia are expected to excrete a dilute urine, resulting in the correction of hyponatremia. Increasing salt intake may also help correct the hyponatremia in patients with SIADH, because the increase in the number of excreted effective osmoles increases the urine volume. These patients however, fail to excrete a dilute urine.

Hypouricemia and increased  $FE_{Urate}$  in patients with SIADH are thought to be due increased renal clearance of urate because of EABV expansion due to water retention, an effect of V1 receptor activation by AVP and perhaps also an effect of chronic hyponatremia.<sup>90–94</sup> Correction of hyponatremia in these patients with water restriction results in normalization of the  $FE_{Urate}$ .<sup>91,92,95</sup>

Debate continues about the existence and true prevalence of the syndrome of cerebral salt wasting.<sup>96–98</sup> A high  $FE_{Urate}$  was observed in patients who were thought to have cerebral salt wasting and in a subset of patients with renal salt wasting who did not have an intracranial lesion.<sup>99–103</sup> The suggested pathophysiology in these patients is the release of a yet unidentified circulating factor that inhibits the reabsorption of  $Na^+$  and of urate in the PCT.

In few reported cases, the  $FE_{Urate}$  remained elevated in patients who were thought to have cerebral/renal salt wasting after correction of hyponatremia with infusion of saline that resulted in the excretion of dilute urine. Hence, it was suggested that the  $FE_{Urate}$  after correction of hyponatremia may differentiate patients with SIADH from those with cerebral salt wasting/renal salt wasting. Because this difference becomes only apparent after the correction of hyponatremia, it has limited utility in helping clinicians to decide what is the correct diagnosis and what is the appropriate therapy.



**Figure 3.** Urine data in the clinical diagnosis of the patients with hyperchloremic metabolic acidosis (HCMA). The concentration of ammonium ( $\text{NH}_4^+$ ) in the urine can be estimated by dividing the urine (U) osmolal gap by 2, the rate of excretion of  $\text{NH}_4^+$  can be calculated by multiplying the  $\text{U}_{\text{NH}_4}/\text{U}_{\text{Creatinine}}$  by the estimated rate of excretion of creatinine in the patient. A rate of excretion of  $\text{NH}_4^+ > 50 \text{ mmol/d}$  suggests that renal tubular acidosis (RTA) is not the cause of the HCMA. In patients with HCMA and a high rate of excretion of  $\text{NH}_4^+$ , one can determine whether an anion other than chloride is being excreted with  $\text{NH}_4^+$  in the urine by comparing the concentrations of sodium and potassium in the urine ( $\text{U}_{\text{Na}} + \text{U}_{\text{K}}$ ) versus that of chloride ( $\text{U}_{\text{Cl}}$ ). The urine pH may provide a clue to suggest the pathophysiology causing a low rate of excretion of  $\text{NH}_4^+$ . A urine pH  $> 6$  suggests a defect in bicarbonate ( $\text{HCO}_3^-$ ) reabsorption in the proximal convoluted tubule (early phase of proximal RTA [pRTA]) or a defect in  $\text{H}^+$  secretion in the distal nephron. Urine citrate excretion is not low in the former group. The pathophysiology causing decreased net  $\text{H}^+$  secretion in the distal nephron can be determined by measuring the  $\text{P}_{\text{CO}_2}$  in alkaline urine ( $\text{U}_{\text{PCO}_2}$ ). ATPase, adenosine 5'-triphosphatase; dRTA, distal RTA; GFR, glomerular filtration rate; PCT, proximal convoluted tubule; SAO, Southeast Asian ovalocytosis.

### Patients With HCMA

There are 2 major pathophysiological mechanisms for the development of HCMA: the direct loss of  $\text{NaHCO}_3$  (i.e.,  $\text{Na}^+$  and  $\text{HCO}_3^-$  are both lost via the same route) and the indirect loss of  $\text{NaHCO}_3$  (i.e.,  $\text{Na}^+$  and  $\text{HCO}_3^-$  are lost via 2 different routes).

A direct loss of  $\text{NaHCO}_3$  may occur via the gastrointestinal tract. Because the capacity of the  $\text{Cl}^-/\text{HCO}_3^-$  anion exchanger in the colon normally exceeds that of the  $\text{Na}^+/\text{H}^+$  exchanger,  $\text{NaHCO}_3$  may be lost in stools if there is a large increase in the delivery of  $\text{NaCl}$  to the colon in a patient with diarrhea. If there is also increased production of organic acids in the colon in these patients,  $\text{HCO}_3^-$  may be titrated by  $\text{H}^+$  of these acids, and  $\text{Na}^+$  (or  $\text{K}^+$ ) ions are lost in the stool with the anions of these organic acids. In either case, there is a loss of  $\text{NaHCO}_3$ .

A direct loss of  $\text{NaHCO}_3$  through the urine occurs in patients in the early phase of a disease process that causes proximal renal tubular acidosis (pRTA).

An indirect loss of  $\text{NaHCO}_3$  could be the result of 2 different groups of disorders. In the first group, there is

overproduction of an acid and a high rate of excretion of its anion in the urine, either because these anions are filtered and also secreted by the PCT (e.g., hippurate anions of hippuric acid produced from toluene metabolism in people who sniff glue)<sup>104</sup> or because the anions are filtered and an appreciable quantity is not reabsorbed in the PCT (e.g.,  $\beta$ -hydroxybutyrate in some patients with diabetic ketoacidosis, and D-lactate in patients with D-lactic acidosis). Although the rate of  $\text{NH}_4^+$  excretion is high in these patients, the rate of excretion of anions exceeds that of  $\text{NH}_4^+$ , and some of the anions are excreted in the urine with  $\text{Na}^+$  and/or  $\text{K}^+$ . Hence, there is an indirect loss of  $\text{NaHCO}_3$ :  $\text{HCO}_3^-$  is lost by titration with  $\text{H}^+$  of the added acid, and  $\text{Na}^+$  is lost by excretion in the urine with the anions of the acid.

In the second group, the major defect is a low rate of  $\text{NH}_4^+$  excretion that is insufficient to generate enough  $\text{HCO}_3^-$  to replace  $\text{HCO}_3^-$  lost in buffering the daily acid load of sulfuric acid produced from the metabolism of sulfur-containing amino acids. This is another form of renal tubular acidosis, labeled as distal RTA.



The initial step in the differential diagnosis in patients with HCMA is to assess the rate of  $\text{NH}_4^+$  excretion, which is expected to be high in patients with gastrointestinal loss of  $\text{HCO}_3^-$  and in those with overproduction of an acid with a high rate of excretion of its anion in the urine, and to be low in patients with distal RTA (Figure 3). Of note, while pRTA in its initial phase is a  $\text{NaHCO}_3$  wasting disease, the metabolic acidemia in the chronic steady state of this disorder seems to be maintained by a low rate of  $\text{NH}_4^+$  excretion. A study in patients with isolated autosomal-dominant pRTA showed that the rate of  $\text{NH}_4^+$  excretion was “normal” in the steady state (in fact, low considering the presence of chronic acidemia), and failed to rise appropriately in response to ammonium chloride ( $\text{NH}_4\text{Cl}$ ) loading.<sup>105</sup> It is postulated that the lesion that impairs the reabsorption of  $\text{HCO}_3^-$  in the PCT results in an alkaline intracellular pH, which inhibits the activity of some key enzymes in glutamine metabolism.<sup>106,107</sup>

### Assess the Rate of $\text{NH}_4^+$ Excretion

The urine pH is not a reliable indicator for the rate of  $\text{NH}_4^+$  excretion.<sup>108,109</sup> In acute acidosis, distal  $\text{H}^+$  secretion is stimulated, but there is a lag period before  $\text{NH}_4^+$  production is increased; the urine pH is low, but there is only a modest increase in  $\text{NH}_4^+$  excretion. In chronic acidosis,  $\text{NH}_4^+$  production and the transfer of  $\text{NH}_3$  into the lumen of the collecting duct are increased; a high rate of  $\text{NH}_4^+$  excretion is achieved while the urine pH rises to  $\sim 6$  as more  $\text{NH}_3$  becomes available to titrate the  $\text{H}^+$  ions.

Because a direct assay for urine  $\text{NH}_4^+$  is not often available in clinical settings, indirect tests are used to estimate the  $\text{NH}_4^+$  excretion rate in patients with HCMA. Although these tests provide only semi-quantitative estimates, this is adequate for clinical use because the information needed is whether the rate of  $\text{NH}_4^+$  excretion is low enough that a defect in renal  $\text{NH}_4^+$  excretion is the cause of the metabolic acidosis or whether it is sufficiently high that another cause of the HCMA should be considered. Normal individuals consuming a typical Western diet excrete 30 to 40 mmol of  $\text{NH}_4^+$  per day, whereas  $\text{NH}_4^+$  excretion rose to  $>200$  mmol/d in normal individuals who were given an acid load of  $\text{NH}_4\text{Cl}$  for several days.<sup>110,111</sup>

### The Urine Anion Gap

The urine anion gap ( $U_{\text{Anion gap}}$ ), calculated as  $(U_{\text{Na}} + U_{\text{K}} - U_{\text{Cl}})$ , has been used to assess the rate of  $\text{NH}_4^+$  excretion in patients with HCMA. The rationale behind this calculation is that if the rate of  $\text{NH}_4^+$  excretion is high and  $\text{NH}_4^+$  is excreted with  $\text{Cl}^-$  (as is the case in patients with gastrointestinal loss of  $\text{HCO}_3^-$ ),  $U_{\text{Cl}}$  will exceed  $(U_{\text{Na}} + U_{\text{K}})$  (a negative value of the  $U_{\text{Anion gap}}$ ).

In contrast, if there is a defect in  $\text{NH}_4^+$  excretion,  $(U_{\text{Na}} + U_{\text{K}})$  will exceed  $U_{\text{Cl}}$  (a positive value of the  $U_{\text{Anion gap}}$ ). There are 2 issues with using the  $U_{\text{Anion gap}}$  that should be noted.

First, the equation that describes the relationship between the rate of  $\text{NH}_4^+$  excretion and the  $U_{\text{Anion gap}}$ , which was based on measurements from 24-hour urine collections, had a constant of 82 (Equation 2).<sup>112</sup>

$$\text{NH}_4^+ \text{ excretion} = -0.8(\text{urine anion gap}) + 82 \quad (2)$$

This constant represents the difference between the rates of excretion of other unmeasured anions and other unmeasured cations in the urine in individuals described as consuming a “normal” diet. Therefore, if  $U_{\text{Cl}}$  exceeds  $(U_{\text{Na}} + U_{\text{K}})$ , one assumes that  $\text{NH}_4^+$  excretion is  $>82$  mEq/d, and hence, RTA is not the cause of the metabolic acidosis. The validity of this assumption is rather questionable, because the rate of excretion of unmeasured anions in the urine may vary considerably depending on dietary intake.<sup>113</sup>

The use of the  $U_{\text{Anion gap}}$  in spot urine samples was examined in a study of patients with RTA, patients with diarrhea, and normal individuals given an acid load of  $\text{NH}_4\text{Cl}$  for 3 days.<sup>114</sup> All patients with RTA had a positive value for the  $U_{\text{Anion gap}}$ , and patients with diarrhea and normal individuals given  $\text{NH}_4\text{Cl}$  had a negative value. The correlation between the value of the  $U_{\text{Anion gap}}$  and the concentration of  $\text{NH}_4^+$  in the urine ( $U_{\text{NH}_4}$ ), however, was only 0.72.  $\text{NH}_4^+$  excretion rates were not reported, but based on the data provided on  $U_{\text{NH}_4}$  in a Figure in the paper,  $\text{NH}_4^+$  excretion seemed to be lower than expected in some of the participants given  $\text{NH}_4\text{Cl}$  and some patients with diarrhea. Three of the 7 normal participants given  $\text{NH}_4\text{Cl}$  had  $U_{\text{NH}_4} < 30$  mmol/l. Four of the 8 patients with diarrhea had  $U_{\text{NH}_4}$  approximately or  $< 30$  mmol/l, and the  $U_{\text{NH}_4}$  in 2 of these patients was in the range observed in the patients with RTA.

The second issue is that the  $U_{\text{Anion gap}}$  detects  $\text{NH}_4^+$  only if it is excreted with  $\text{Cl}^-$ . Hence, if  $\text{NH}_4^+$  is excreted with another anion (e.g., hippurate,  $\beta$ -hydroxy butyrate, D-lactate), the  $U_{\text{Anion gap}}$  will fail to detect a high rate of  $\text{NH}_4^+$  excretion, and these patients may be misdiagnosed as RTA.

### The Urine Osmolal Gap

The urine osmolal gap ( $U_{\text{Osmolal gap}}$ ) may provide a better indirect test to assess the rate of  $\text{NH}_4^+$  excretion in patients with HCMA.<sup>115–118</sup> The  $U_{\text{Osmolal gap}}$  is calculated as the difference between the measured  $U_{\text{Osm}}$  and the  $U_{\text{Osm}}$  calculated from  $2(U_{\text{Na}} + U_{\text{K}}) + U_{\text{Urea}} + U_{\text{Glucose}}$  (if hyperglycemia is present). Multiplying  $(U_{\text{Na}} + U_{\text{K}})$  by 2, accounts for their accompanying anions. This overestimates the actual number of

osmoles in the urine because some of these anions (e.g.,  $\text{SO}_4^{2-}$ , citrate $^{2-}$ , and perhaps some other organic anions) are not monovalent. On the other hand, the calculation of the  $U_{\text{Osm}}$  underestimates the actual number of urine osmoles because it does not include calcium and magnesium and their accompanying anions.

Meregalli *et al.*<sup>119</sup> in a study in normal individuals and Raphael and Xi<sup>120</sup> in a study in kidney transplant recipients, a small subset of whom had HCMA, noted poor correlation between the value of the  $U_{\text{Osmolal gap}}$  and the concentration of  $\text{NH}_4^+$  in the urine. We emphasize that the purpose of the calculation of the  $U_{\text{Osmolal gap}}$  is not to determine the actual concentration of  $\text{NH}_4^+$  in the urine but rather to assess if the rate of excretion of  $\text{NH}_4^+$  in a patient with HCMA is sufficiently high that a cause for the HCMA other than RTA should be considered.<sup>118</sup>

The  $U_{\text{Osmolal gap}}$  detects  $\text{NH}_4^+$  in the urine regardless of its accompanying anion.<sup>104,116</sup> The  $U_{\text{Osmolal gap}}$  is unreliable to assess the rate of  $\text{NH}_4^+$  excretion if other osmoles (e.g., ethanol, methanol, ethylene glycol, mannitol) are present in the urine.

The concentration of  $\text{NH}_4^+$  in the urine can be estimated by dividing the  $U_{\text{Osmolal gap}}$  by 2, and the rate of  $\text{NH}_4^+$  excretion can be calculated by multiplying the  $U_{\text{NH}_4}/U_{\text{Creatinine}}$  by the estimated rate of excretion of creatinine in the patient. An estimated rate of  $\text{NH}_4^+$  excretion  $>50$  mmol/d suggests that RTA is not likely to be the cause of the HCMA.

### Urinary Tests to Determine the Cause of Low $\text{NH}_4^+$ Excretion

The low rate of  $\text{NH}_4^+$  excretion could be due to decreased availability of  $\text{NH}_3$  in the lumen of the collecting duct, because of decreased  $\text{NH}_4^+$  production, a defect in  $\text{NH}_4^+$  transfer to the medullary interstitium, or  $\text{NH}_3$  transfer to the lumen of the collecting duct via the nonerythroid Rhesus glycoproteins Rhbg and Rhcg, and/or decreased net rate of  $\text{H}^+$  secretion in the distal nephron.<sup>107,121,122</sup>

A low rate of  $\text{NH}_4^+$  production may be due to alkalization of PCT cells because of hyperkalemia or a genetic or an acquired disorder that compromises proximal  $\text{H}^+$  secretion or the exit of  $\text{HCO}_3^-$  from PCT cells, also causing reduced capacity to reabsorb  $\text{HCO}_3^-$  (i.e., pRTA). pRTA typically occurs in patients with Fanconi syndrome, in which other  $\text{Na}^+$ -linked transport functions of PCT are affected, leading to renal glucosuria, aminoaciduria, citraturia, and increased fractional excretion rates of phosphate and urate. The common causes of Fanconi syndrome are paraproteinemia in adults and cystinosis in children.<sup>123</sup>

A low net rate of  $\text{H}^+$  secretion in the distal nephron could be due to an  $\text{H}^+$ -adenosine 5'-triphosphatase defect (e.g., autoimmune and hypergammaglobulinemic disorders, including Sjögren syndrome), back-leak of  $\text{H}^+$  (e.g., due to drugs such as amphotericin B), or a disorder associated with the distal secretion of  $\text{HCO}_3^-$  (e.g., in some patients with Southeast Asian ovalocytosis who have a second mutation in the  $\text{Cl}^-/\text{HCO}_3^-$  anion exchanger causing it to be mis-targeted to the luminal membrane of  $\beta$ -intercalated cells).

The following urinary tests may help to determine the basis of the low rate of  $\text{NH}_4^+$  excretion (Figure 3):

**The Urine pH.** The urine pH should be measured with a pH meter in a freshly collected urine sample, or in a urine sample collected under mineral oil, to minimize diffusion of  $\text{CO}_2$ , if there will be a delay in performing the measurement. The basis for the low rate of  $\text{NH}_4^+$  excretion may be deduced from the urine pH.<sup>107</sup> A urine pH of  $\sim 5$  suggests a defect causing a low rate of  $\text{NH}_4^+$  production or impairing the accumulation of  $\text{NH}_4^+$  in the medullary interstitium/transfer of  $\text{NH}_3$  to the lumen of the MCD. A urine pH  $>6$  suggests a defect in  $\text{HCO}_3^-$  reabsorption in the PCT (early phase of pRTA) or a defect in  $\text{H}^+$  secretion in the distal nephron.

**The Rate of Citrate Excretion.** The usual rate of citrate excretion is  $\sim 2$  mmol/d. The rate of citrate excretion provides a window into the pH in PCT cells.<sup>124–126</sup> Patients with metabolic acidosis have hypocitraturia, partly because of the effect of the lower pH in PCT cells to stimulate the reabsorption of citrate.<sup>124,127–129</sup> Citrate excretion however, is not low in patients with pRTA because of decreased citrate reabsorption as a result of an alkaline PCT cell pH and/or as a component of Fanconi syndrome.<sup>105,106</sup> An alkaline urine pH in this setting suggests the diagnosis of pRTA in the initial phase. Citrate excretion was reported to be also not low in a patient with carbonic anhydrase II deficiency.<sup>130</sup> Different from inhibition of luminal carbonic anhydrase IV by acetazolamide, which is associated with marked hypocitraturia, deficiency of the cytoplasmic carbonic anhydrase II leads to an alkaline pH in PCT cells, which decreases the metabolism of citrate in PCT cells and subsequently decreases citrate reabsorption. Carbonic anhydrase II deficiency involves also the distal nephron causing decreased distal  $\text{H}^+$  secretion.<sup>130,131</sup>

**The  $\text{Pco}_2$  in Alkaline Urine.** The urinary  $\text{Pco}_2$  is used to assess  $\text{H}^+$  secretion in the distal nephron.<sup>132–134</sup> The patient is given a load of  $\text{NaHCO}_3$  to increase the filtered load of  $\text{HCO}_3^-$  and its delivery to the distal nephron. Secretion of  $\text{H}^+$  by the MCD leads to the formation of carbonic acid ( $\text{H}_2\text{CO}_3$ ). Because there is no

luminal carbonic anhydrase,  $\text{H}_2\text{CO}_3$  is dehydrated slowly to  $\text{CO}_2 + \text{H}_2\text{O}$ . Urinary  $\text{Pco}_2$  close to 70 mm Hg suggests a normal rate of net  $\text{H}^+$  secretion in the distal nephron.

Despite a defect in distal  $\text{H}^+$  secretion, the urinary  $\text{Pco}_2$  is high in patients with a lesion that leads to  $\text{H}^+$  back-leak.<sup>135</sup> This is because as more  $\text{HCO}_3^-$  is delivered distally, it traps  $\text{H}^+$  and prevents its back-leak. The urinary  $\text{Pco}_2$  is also high in patients with disorders that cause  $\text{HCO}_3^-$  secretion in the distal nephron (e.g., some patients with SOA).<sup>136,137</sup> This is because secretion of  $\text{HCO}_3^-$  into the lumen of the distal nephron during  $\text{HCO}_3^-$  loading raises the luminal fluid pH, causing  $\text{H}^+$  to be released from monovalent phosphate ( $\text{H}_2\text{PO}_4^-$ ), these  $\text{H}^+$  react with luminal  $\text{HCO}_3^-$  and form  $\text{H}_2\text{CO}_3$ .

FE of  $\text{HCO}_3^-$ . The FE of  $\text{HCO}_3^-$  is used to assess  $\text{H}^+$  secretion by the PCT.<sup>138</sup>  $\text{NaHCO}_3$  is given to raise the plasma  $\text{HCO}_3^-$  to the normal range. If there is a defect in  $\text{H}^+$  secretion in the PCT, the filtered load of  $\text{HCO}_3^-$  will exceed the capacity for its reabsorption, and  $\text{HCO}_3^-$  will be spilled in the urine; hence the urine pH becomes alkaline with values  $>7$ , and the FE of  $\text{HCO}_3^-$  exceeds 15%.

This test is usually not needed. These patients will be recognized clinically by failure to correct their metabolic acidemia despite large doses of  $\text{NaHCO}_3$ .

## DISCLOSURE

The authors declared no competing interests.

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