American Society of Nephrology Quiz and Questionnaire 2013: Electrolyte and Acid-Base

Biff F. Palmer,* Mark A. Perazella,† and Michael J. Choi‡

Abstract
The Nephrology Quiz and Questionnaire (NQ&Q) remains an extremely popular session for attendees of the annual meeting of the American Society of Nephrology. As in past years, the conference hall was overflowing with interested audience members. Topics covered by expert discussants included electrolyte and acid-base disorders, glomerular disease, ESRD/dialysis, and transplantation. Complex cases representing each of these categories along with single-best-answer questions were prepared by a panel of experts. Prior to the meeting, program directors of United States nephrology training programs answered questions through an Internet-based questionnaire. A new addition to the NQ&Q was participation in the questionnaire by nephrology fellows. To review the process, members of the audience test their knowledge and judgment on a series of case-oriented questions prepared and discussed by experts. Their answers are compared in real time using audience response devices with the answers of nephrology fellows and training program directors. The correct and incorrect answers are then briefly discussed after the audience responses, and the results of the questionnaire are displayed. This article recapitulates the session and reproduces its educational value for the readers of CJASN. Enjoy the clinical cases and expert discussions.


Introduction: Mark A. Perazella and Michael J. Choi (Comoderators)
For most American Society of Nephrology Kidney Week attendees, case-based clinical nephrology talks are the most exciting venues of the meeting. The Nephrology Quiz and Questionnaire (NQ&Q) is the essence of clinical nephrology and represents what drew many of us into the field of nephrology. The 2013 NQ&Q in Atlanta, Georgia, with full-house attendance, was no exception. Each of the discussants prepared vignettes of puzzling cases, each illustrating some topical, challenging, or controversial aspect of the diagnosis or management of various areas of nephrology. These eight interesting cases were presented and eloquently discussed by our four expert The American Society of Nephrology (ASN) faculty. Subsequently, each discussant prepared a manuscript summarizing his or her discussion of the cases, which serves as the main text of this article.

In this NQ&Q, Dr. Biff Palmer presents his two challenging electrolyte/acid-base cases and eloquently synthesizes the available data to make the correct diagnosis. The audience responses are reviewed along with the responses of training program directors and nephrology fellows obtained before the meeting. This review provides an interesting perspective into the thought processes of nephrologists with varying levels of training and experience. Dr. Palmer reviews essential clinical and laboratory data available in the cases and walks the reader through the diagnosis and appropriate management of these two complicated and challenging electrolyte/acid-base cases. Overall, an educational experience was had by all participants. We hope that this “distillate” from Atlanta will serve the CJASN subscribers well and provide some fresh insights into the complexity and vibrancy of clinical nephrology for those who were unable to attend the meeting (Mark A. Perazella, MD, Yale University, Comoderator, and Michael Choi, MD, Johns Hopkins University, Comoderator).

Electrolyte Case 1: Biff F. Palmer (Discussant)
A 19-year-old woman is transported to the emergency department after being found on the floor of her apartment unable to move. The patient states she was in her usual state of health until 36 hours earlier, when she noticed the onset of episodic but progressively worsening generalized weakness. There was no history of bladder or bowel incontinence or loss of consciousness. Medical history was unremarkable, and the patient reported no ingestions; however, the roommate who was unable to attend the meeting (Mark A. Perazella, MD, Yale University, Comoderator, and Michael Choi, MD, Johns Hopkins University, Comoderator).


*Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; †Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut; and ‡Division of Nephrology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland

Correspondence: Dr. Biff F. Palmer, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390. Email: biff.palmer@utsouthwestern.edu
Table 1. Laboratory data for Case 1

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<tr>
<td>Urine osmolality (mOsm/kg)</td>
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Question 1
Which one of the following best describes the acid-base findings in this case?

A. Proximal renal tubular acidosis
B. Renal tubular acidosis of renal insufficiency
C. Overproduction of an organic acid
D. Distal renal tubular acidosis

Discussion of Case 1
This 19-year-old woman presents with severe weakness in the setting of hypokalemia and metabolic acidosis resulting from deliberate inhalation of toluene. As discussed in more detail below, the mechanism by which the acid-base disturbance develops in this setting can best be described as overproduction of an organic acid, making choice C the correct answer (Figure 1). Signs of inhalant abuse include drying and redness around the mouth and nose, spots or sores around the mouth, and red or runny eyes or nose. Inhalant abuse now includes a broad range of volatile solvents and gas products to include model airplane glue, paint thinner, gasoline, and nail polish remover.

Examination of the metabolic profile discloses evidence of a triple acid-base disturbance composed of anion gap metabolic acidosis, hyperchloremic normal gap metabolic acidosis, and respiratory acidosis. One should systematically interpret serum chemistries in order to identify the overt and, more important, the subtle abnormalities that may exist in a laboratory report (1).

In this regard, a useful starting point is to first examine the serum Na⁺ concentration in order to determine whether a disturbance in the plasma tonicity is present. This patient’s serum Na⁺ is mildly reduced, suggesting a relative excess of free water. Despite the downward trend in Na⁺, the serum Cl⁻ concentration is increased. Changes in hydration status alone will cause the serum Cl⁻ to change in parallel and to the same extent as the serum Na⁺ concentration. Whenever the serum Cl⁻ moves in a direction opposite or changes disproportionately to the change in serum Na⁺, an acid-base disorder is suggested. In this patient, the serum Cl⁻ is increased with respect to the serum Na⁺, suggesting the presence of chronic respiratory alkalosis or normal anion gap metabolic acidosis (2).

The next step is to calculate the serum anion gap. Calculation of the anion gap should be a routine part of the examination of every set of electrolytes, no matter how normal the individual values may appear. In this case, the anion gap is 21 mEq/L, thus identifying the presence of an anion gap metabolic acidosis as at least one of the acid-base disturbances in this case.

Given the anion gap metabolic acidosis, the next step is to determine whether the measured serum HCO₃⁻ is equal to the predicted serum HCO₃⁻. In general, the serum HCO₃⁻ concentration will fall by an amount equal to the increase in anion gap. Assuming a normal value of 12, the anion gap has increased by 9 in this patient. One would
predict the serum HCO$_3^-$ should be approximately 15 mEq/L, assuming a normal value of 24 mEq/L (24–9=15). Because the measured value is 10 mEq/L, one can conclude that a normal gap hyperchloremic metabolic acidosis is also present, as suggested by the disproportionate rise in serum Cl$^-$ concentration noted above. The expected respiratory compensation for a measured HCO$_3^-$ of 10 mEq/L in the setting of metabolic acidosis would be a pCO$_2$ of approximately 25 mmHg. The measure value of 35 mmHg indicates insufficient respiratory compensation and confirms the presence of respiratory acidosis. The remainder of the discussion will focus on the cause of each of the acid-base disorders identified in this patient with toluene abuse.

The metabolism of toluene in the liver leads to the generation of benzoic and hippuric acid such that one H$^+$ is added to the body for every toluene metabolized (3). These acids are buffered by endogenous bicarbonate to form the respective Na$^+$ salts of the acids and CO$_2$, the latter of which is eliminated by the lungs. As long as extracellular volume is near normal, hippurate will be rapidly excreted by the kidney by both filtration and secretion as sodium and potassium salts. Excretion of these salts is equivalent to the loss of potential bicarbonate. This loss of potential bicarbonate in the urine at the same time the kidney is retaining dietary NaCl results in a hyperchloremic normal gap acidosis.

If the rate of hippurate production exceeds urinary elimination the anion will accumulate in the serum and be reflected by an increase in the serum anion gap (4). Patients with toluene abuse who present with some degree of anion gap metabolic acidosis tend to be more acidemic, be slightly hyponatremic, and show evidence of a concomitant hyperchloremia (5). Extrarenal causes of metabolic acidosis are associated with an appropriate increase in net acid excretion, primarily reflected by high levels of urinary ammonium excretion. By contrast, net acid excretion and urinary ammonium levels are low in metabolic acidosis of renal origin. Unfortunately, measurement of urinary ammonium is not a test that is commonly available in clinical medicine, although direct measurement of ammonium in the urine may soon become available as a commercial test (6). One can indirectly assess the amount of urinary ammonium by calculating the urinary anion gap (UAG):

$$UAG = (\text{Urine } Na^+ + \text{Urine } K^+) - \text{Urine } Cl^-$$

Under normal circumstances the UAG is positive, with values ranging from 30 to 50. A negative value for the UAG suggests the presence of increased renal excretion of an unmeasured cation, a cation other than Na$^+$ or K$^+$. One such cation is NH$_4^+$. Metabolic acidosis of extrarenal origin is associated with a marked increase in urinary ammonium excretion, and therefore a large negative value will be obtained for the UAG. If the acidosis is of renal origin, urinary ammonium excretion will be minimal and the UAG will usually be positive.

The UAG in this patient is 15, suggesting the acidosis is due to intrinsic renal disease. However, one setting in which the UAG may not be useful is when there is increased excretion of Na$^+$ coupled to a non-Cl$^-$ anion. For example, in this patient the UAG may be positive because of increased urinary excretion of Na$^+$ and K$^+$ coupled to hippurate and benzoate. Over time, as ammoniagenesis progressively increases as a result of the stimulatory effects of acidemia and hypokalemia, large quantities of ammonium hippurate and benzoleate will be excreted. This further limits the utility of the UAG to detect urinary ammonia excretion.

A useful method to semiquantitatively estimate the amount of ammonium in the urine under conditions of organic acid anion loss in the urine is to measure the urine osmolar gap (8). The urine osmolar gap is defined as the difference between measured urine osmolality and an estimate of the urine osmolality as derived from the following equation:

$$U_{osm}(\text{mosmol/kg}) = \left(2 \times [Na^+ + K^+]\right) + (\text{urea nitrogen} \text{ (mg/dl)/2.8}) + (\text{glucose} \text{ (mg/dl)/18})$$

If the urine dipstick is negative, glucose can be omitted from the equation. Normally, this gap is 10–100 mOsmol/kg, with excretion of ammonium and its accompanying anions accounting for half of this value. In this case, the urine osmolality gap is 436 mOsmol/kg, which predicts a urine ammonium excretion of approximately 218 mEq/L. Thus, urinary ammonium excretion is robust in this patient, arguing against an acidosis of renal origin, making choices A, B, and D incorrect.

The severe hypokalemia on admission accounts for the severe weakness on presentation. The blunted respiratory response to the metabolic acidosis is another manifestation of this weakness and has been previously reported in toluene abuse (9–11). Renal K$^+$ wasting is due to the poorly reabsorbable anion effect of hippurate and benzoate, causing increased distal Na$^+$ delivery in the setting of increased mineralocorticoid activity, the latter being driven by volume depletion (12). It should be noted the total body deficit of K$^+$ is even greater than that suggested by the serum
K⁺ concentration given the effect of acidosis and in particular normal gap acidosis to shift K⁺ out of the cell. In this regard therapy should be directed toward correcting the K⁺ deficit using intravenous fluid initially devoid of bicarbonate and glucose so as to avoid worsening of the hypokalemia.

**Electrolyte Case 2: Biff F. Palmer (Discussant)**

You are asked to consult on a 58-year-old man with hyponatremia. The patient has been paralyzed from the waist down secondary to a gunshot wound 2 years ago. Over the past 6 months he has developed decubitus ulcers over each sacrum that are refractory to conservative management. He was admitted 7 days ago for ongoing management. Laboratory data on admission were normal. Six days ago, 0.75 kg of granulated sugar was poured into each wound in an attempt to promote wound healing. The wounds were inspected twice daily, and additional sugar was applied to keep the wound cavities completely filled. Over the last 2 days, the patient has developed decreased oral intake. One day ago, urine output decreased and he was started on 0.9% saline at a rate of 75 ml/hr. Routine laboratory results obtained today are given in Table 2.

**Question 2A**
Which one of the following choices provides the most likely explanation for the disturbance in serum sodium concentration in this patient?

A. Hypotonic hyponatremia  
B. Hypertonic hyponatremia  
C. Pseudohyponatremia  
D. Isotonic hyponatremia

**Question 2B**
Which one of the following would most likely be present on renal biopsy?

A. Tubular necrosis  
B. Vacuolization of tubular cells  
C. Lipofuscin accumulation in tubular cells  
D. Myelin bodies in tubular cells

**Discussion of Case 2**
The patient has hypertonic hyponatremia (choice B) resulting from the subcutaneous absorption of sucrose (Figure 2). After direct absorption into the systemic circulation, sucrose cannot undergo hydrolysis and is excreted in the urine. Similar to hypertonic mannitol, large quantities of hypertonic sucrose are nephrotoxic, resulting in histologic changes characterized by vacuolization of the renal tubular cells, a lesion referred to as osmotic nephrosis (Figure 3).

Hypertonic hyponatremia is caused by abnormally high concentrations of an effective osmole in the circulation that osmotically extracts water from cells, diluting the plasma sodium concentration. Unlike the situation with hypotonic hyponatremia, in which cells are swollen, body cells in hypertonic hyponatremia are dehydrated. Hyperglycemia,

<table>
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<tr>
<td>Cl⁻</td>
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</tr>
</tbody>
</table>

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**Figure 2.** Question 2A: Distribution of answers from fellows in training, training program directors (TPD) and audience members at the Kidney Week meeting. The correct answer is B.
mannitol infusions, and infusions of immunoglobulin preparations containing maltose or sucrose are the most common causes (13).

In this patient, granulated sugar was being applied to the decubitus ulcer cavities in an attempt to promote wound healing. The application of sugar or honey to various types of wounds has been practiced for years. The precise mechanism by which this strategy may be of benefit is not known; however, both substances exert antimicrobial effects and promote formation of granulation tissue (14–16).

When sucrose is ingested orally, it is broken down to dextrose and fructose by disaccharidases in the gut and the monosaccharides are absorbed separately. After direct absorption into the systemic circulation, sucrose cannot undergo hydrolysis and can only be excreted in the urine as the intact molecule. The diuretic effect of intravenous infusions of hypertonic sucrose solutions was commonly exploited in clinical practice 30–40 years ago to treat hypotension, cerebral edema, and a variety of edematous states (17). Initially in experimental animals and later in humans, such infusions were associated with renal histologic changes characteristic of what has subsequently come to be known as osmotic nephrosis (18). The mechanism by which high concentrations of sucrose lead to renal tubular injury is not known. Radioactive tracer studies in rats suggest that sucrose is pinocytosed into renal tubular cells, where it is then incorporated into phagolysosomes (19). The intracellular accumulation of sucrose then leads to vacuole formation and cellular swelling as a result of osmotic induced water movement.

As renal injury develops and the GFR declines, sucrose will begin to accumulate in the extracellular fluid space and begin to exert an osmotic effect, resulting in translocational hyponatremia. This movement of water from the intracellular to extracellular space can also give rise to hyperkalemia by way of solvent drag or passive diffusion (20). Although not provided in this case, the difference between the measured and calculated serum osmolality would reveal a significant osmolar gap due to accumulation of sucrose in the extracellular space. Prior reports have described AKI and hyponatremia resulting from wounds packed with granulated sugar (21,22). In one patient, the serum Na+ was 119 mmol/L in the setting of a measured plasma osmolality of 315 mOsm/kg, giving rise to an osmolar gap of 49 mOsm/kg.

An example of isotonic hyponatremia (choice D) is the systemic absorption of isosmotic irrigants during prostate or intrauterine surgery. In these cases, the solute responsible for the low serum sodium concentration is rapidly absorbed with water so that the plasma osmolality is not increased and there is no shift of water from cells. Rather, there is an expansion of the extracellular space with fluid, and, as long as the absorbed solute remains extracellular, the water that is absorbed with the solute remains extracellular as well, diluting the plasma sodium concentration.

Pseudohyponatremia (choice C) refers to hyponatremia in the setting of hyperproteinemia or hyperlipidemia. Under normal conditions plasma is normally 93% water and 7% proteins and lipids. With excess accumulation of plasma protein or triglycerides, the fraction of the plasma that is aqueous is decreased, such that each volume of plasma measured will contain less Na+ because Na+ is present only in plasma water. Automated clinical laboratory determinations using indirect potentiometry will report an artifically low plasma Na+ concentration despite a normal Na+ concentration in plasma water. With indirect potentiometry the plasma sample is diluted before the actual measurement is obtained, and the plasma Na+ concentration is then determined by correcting for the dilution degree, making the assumption that plasma water equals 93% of the total sample volume. As a result, the Na+ level determined by indirect potentiometry will be artificially low when the plasma water content is <93%. Instruments used for measuring arterial blood gases use direct potentiometry without any dilution and measure the activity of sodium in the water phase only. Thus, pseudohyponatremia does not occur when the measurement is made with direct potentiometry. Hypotonic hyponatremia (choice A) refers to a low Na+ concentration and low plasma osmolality and is associated with swelling of all body cells.
With regard to the other choices in the second question, lipofuscin (choice C) refers to finely granular yellow-brown pigment granules composed of lipid containing residues of lysosomal digestion and is considered a nonspecific marker of aging. Myelin bodies (choice D) refer to dense osmiophilic and coarsely lamellated intralysosomal inclusions found in glomerular, tubular, vascular, and interstitial cells of the kidney. These structures are particularly characteristic of patients with renal involvement in Fabry disease but may also be seen in the setting of gentamicin or other drug toxicity (23,24). Acute tubular necrosis (choice A) would not fit with the other findings in this case.

Disclosures
None.

References

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