American Society of Nephrology Quiz and Questionnaire 2015: Electrolytes and Acid–Base Disorders

Mitchell H. Rosner

Abstract
The Nephrology Quiz and Questionnaire remains an extremely popular session for attendees of the annual Kidney Week meeting of the American Society of Nephrology. During the 2015 meeting the conference hall was once again overflowing with eager quiz participants. Topics covered by the experts included electrolyte and acid–base disorders, glomerular disease, end-stage renal disease and dialysis, and kidney transplantation. Complex cases representing each of these categories together with single-best-answer questions were prepared and submitted by the panel of experts. Before the meeting, training program directors of nephrology fellowship programs and nephrology fellows in the United States answered the questions through an internet-based questionnaire. During the live session members of the audience tested their knowledge and judgment on the same series of case-oriented questions in a quiz. The audience compared their answers in real time using a cell-phone app containing the answers of the nephrology fellows and training program directors. The results of the online questionnaire were displayed, and then the quiz answers were discussed. As always, the audience, lecturers, and moderators enjoyed this highly educational session. This article recapitulates the session and reproduces selected content of educational value for the Clinical Journal of the American Society of Nephrology readers. Enjoy the clinical cases and expert discussions.


Introduction: Mark A. Perazella and Michael J. Choi (Comoderators)
For most attendees of the American Society of Nephrology Kidney Week, case-based clinical nephrology talks are some of the most exciting sessions. The Nephrology Quiz and Questionnaire (NQ&Q) represents the essence of clinical nephrology, and highlights the skills and challenges that drew all of us into the field of nephrology. This year’s NQ&Q in beautiful San Diego, with full-house attendance, was no exception. The four American Society of Nephrology faculty experts prepared vignettes of puzzling cases to illustrate the topical, challenging, or controversial aspects of the diagnosis or management of key clinical areas of nephrology. These eight interesting cases were presented and eloquently discussed during the live session. Subsequently, each expert prepared a manuscript summarizing his or her case discussions, and these manuscripts have been collated for publication.

In this NQ&Q, Dr. Mitchell H. Rosner presents his two challenging electrolyte/acid–base cases and eloquently synthesizes the available data to make the correct diagnosis. The live audience responses are reviewed together with the training program director and nephrology fellow responses obtained prior to the meeting, giving an interesting perspective into the thought processes of nephrologists with varying levels of training and experience. Dr. Rosner reviews the available clinical and laboratory data and walks the reader through the diagnosis and appropriate management of these two challenging electrolyte/acid–base cases. Overall, this was a very educational experience for all participants. We hope that this summary from the San Diego meeting will serve the Clinical Journal of the American Society of Nephrology subscribers well, and provide some fresh insights into the complexity and vibrancy of clinical nephrology for those who were unable to attend the meeting.

Case 1
A 39-year-old black woman received a living unrelated donor kidney transplant approximately 18 months ago. Before transplantation she had been on home hemodialysis for 8 months secondary to end-stage kidney disease from focal segmental glomerulosclerosis. Her post-transplant course is notable for one episode of acute rejection, which was treated successfully with high-dose corticosteroids. Her kidney function over the past 6 months has been stable with an eGFR of 46. Her past medical history is otherwise notable for hypertension, hyperlipidemia, and gastroesophageal reflux. Her blood pressure has been difficult to control. Physical examination is within normal limits without edema. Current medications include: tacrolimus 2 mg twice daily, prednisone 7.5 mg daily, mycophenolate mofetil 1000 mg twice daily, sulfamethoxazole–trimethoprim 400–80 mg three times per week, amlodipine 10 mg daily, carvedilol 25 mg twice daily, omeprazole 20 mg daily, pravastatin 20 mg
daily and nystatin 400,000 units swish and swallow four times daily. Her blood pressure typically runs between 180–160/100–90 mmHg.

Two weeks ago, during routine laboratory work, the following results were obtained (Table 1, initial values). The patient was sent to the emergency room where an electrocardiogram was within normal limits and repeat serum potassium was 5.9 meq/L. At this time, blood pressure was 172/89 mmHg. She received two doses of 30 g sodium polystyrene sulfonate and the following medication changes were instituted: sulfamethoxazole–trimethoprim was discontinued; sodium bicarbonate 650 mg twice daily and furosemide 20 mg daily were initiated.

The patient was seen in follow-up 2 weeks later at which time laboratory work revealed the results shown in Table 1 (follow-up values). Her blood pressure was 169/90 mmHg.

**Question 1A**

Which of the following mechanisms is involved in the development of hyperkalemia and hypertension in this patient?

- a. Depressed GFR
- b. Chronic metabolic acidosis
- c. Upregulation of the sodium–chloride cotransporter in the distal tubule
- d. Upregulation of the aldosterone receptor in the distal tubule
- e. Corticosteroid-induced suppression of aldosterone synthesis

The correct answer is: C. The responses from fellowship program directors, fellows-in-training, and the audience are shown in Figure 1.
of the syndrome of familial hyperkalemia and hypertension (FHHt), also known as pseudohypoaldosteronism type II or Gordon Syndrome (9–11). This syndrome is due to mutations in the WNK (with no K [lysine]) family of proteins, which are widely expressed and promote blood pressure and electrolyte homeostasis through a variety of mechanisms. Members of this complex family of proteins are reported to affect sodium–chloride cotransporters (NCCs), sodium–potassium–chloride cotransporters, potassium–chloride cotransporters, the renal outer medullary potassium channel (ROMK), and the epithelial sodium channel, both directly and indirectly. Mutations in WNK1 and WNK4 were shown to cause FHHt and to ultimately lead to functional increases (via phosphorylation) in the activity of the NCC leading to sodium retention and hypotension (12,13). A complete description of the WNK kinases and their role in blood pressure, sodium and potassium homeostasis is beyond the scope of this paper, and the reader is referred to several comprehensive reviews (13–15).

The direct link between FHHt and the CNI-mediated effects on blood pressure and potassium was established when Hoorn and coworkers determined that tacrolimus stimulates NCC in mice and thereby induces salt-sensitive hypertension. Furthermore, renal biopsy specimens from patients treated with CNIs had increases in NCC and its active phosphorylated form. The mechanism of the tacrolimus-induced stimulation of NCC was similar to that seen in FHHt and, in this case, was due to WNK-3- and WNK-4-mediated effects as well as the more downstream Ste20-related kinase (16). Thus, CNIs, through their effects on WNK proteins, can mimic the phenotype of FHHt resulting in upregulation of NCC with continued sodium reabsorption in the distal tubule, volume expansion and hypertension.

The link between the mechanisms of hyperkalemia in CNI-treated patients and the WNK-mediated activation of NCC is not completely understood. One possible mechanism is shown in Figure 2, where activation of NCC by CNIs leads to near complete reabsorption of sodium so that very little sodium is presented distally to the tubule and thus potassium excretion is limited (through the conjugated functions of sodium reabsorption through the epithelial sodium channel [ENaC] and potassium excretion through ROMK). Furthermore, the tubular lumen also carries less negative charge (a driving force for potassium excretion) due to increased chloride reabsorption by NCC. This mechanism may be augmented by the CNI-induced volume expansion that can decrease renin secretion and downregulate the mineralocorticoid receptor. Another potential contributing factor is the role of intraluminal calcium concentrations; activation of the NCC leads to an increase in luminal calcium, which has been shown to reduce net potassium secretion by decreasing the electrochemical gradient for potassium secretion, probably by inhibiting the activity of ENaC (17,18).

To discuss the incorrect answers, a depressed GFR can certainly contribute to the development of hypertension and hyperkalemia. However, this patient’s GFR was only mildly depressed (eGFR of 41) and thus unlikely to be a major determinant. For example, in the African American Study of Hypertension and Kidney Disease trial of non-diabetic hypertensive patients, the event rate of hyperkalemia in patients with baseline GFRs between 40 and 50 was quite low at <3 per 100 patient-years (although these patients were not on CNIs) (19). Although metabolic acidosis can lead to a rise in serum potassium, it is noteworthy that these effects are highly dependent on the etiology of the metabolic acidosis (for example, diarrhea is often associated with hypokalemia and the various renal tubular acidosis have variable effects on the serum potassium) and attributing significant hyperkalemia, such as seen in this patient, to a mild chronic metabolic acidosis is not likely (20,21). However, hyperkalemia itself can lead to a metabolic acidosis. This may be due to at least two mechanisms: (1) the suppressive effect of hyperkalemia on renal ammoniagenesis, which limits hydrogen ion secretion, and (2) in the setting of limited sodium delivery to

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**Figure 2.** | **Mechanism of CNI-induced hyperkalemia.** Tacrolimus-induced activation of the sodium–chloride cotransporter leads to near complete absorption of sodium and a limitation on the amount of sodium that can be exchanged for potassium in the collecting tubule. Cl⁻, chlorine ion; CNT, collecting tubule; DCT1, distal convoluted tubule; K⁺, potassium ion; Na⁺, sodium ion.
the distal tubule, such as in this case, there is a limit to the degree of luminal electronegativity in the vicinity of the intercalated cells, which decreases the driving force for hydrogen ion secretion. Corticosteroid use suppresses production of adrenal corticosteroids and has a minor effect on aldosterone synthesis and thus would be unlikely to have a major effect on potassium homeostasis unless at high doses and associated with a marked catabolic effect. Heering et al. demonstrated that aldosterone levels did not substantially differ between renal transplant patients and normal controls (8,22). Finally, upregulation of the aldosterone receptor in the distal tubule leads to increased sodium reabsorption as well as increased potassium excretion resulting in either normal or low serum potassium levels.

It should be noted that other investigators have successfully treated CNI-associated hyperkalemia with fludrocortisone at the possible expense of worsening hypertension (23).

Case 1 Continued

Over the next 6 weeks the patient’s furosemide dose was increased to 40 mg a day and the sodium bicarbonate increased to 650 mg three times daily. Her diet was reviewed with a nutritionist. She was also asked to take 15 g of sodium polystyrene sulfonate with her largest meal of the day. Despite these changes, her potassium levels remained between 5.9 and 6.4 meq/L and her blood pressure remained elevated as well.

Question 2

Which one of the following is the next therapy of choice?

a. Sodium polystyrene sulfonate 30 g three times a day
b. Stop tacrolimus and start sirolimus
c. Hydrochlorothiazide 25 mg once a day
d. Acetazolamide 500 mg once a day
e. Spironolactone 25 mg once a day

The correct answer: C. The responses from fellowship program directors, fellows-in-training, and the audience are shown in Figure 3.
metabolic issues seen in transplant patients (such as hypomagnesemia, hyperglycemia and gout), and these risks have to be balanced against the antihypertensive effects of these medications in a given patient.

In the patient described in this case (as well as in other CNI-treated transplant patients), an added benefit of HCTZ is that the serum potassium will also decrease, most likely due to an increase in distal sodium delivery, which enables more potassium excretion through the coordinated functions of ENaC and ROMK.

To discuss the incorrect answers, sodium polystyrene sulfonate is ineffective in treating hypertension and its efficacy in lowering serum potassium levels has been questioned (29). Although switching the patient to sirolimus instead of tacrolimus is a possibility, this might increase the possibility of rejection and simpler, lower-risk alternatives, such as HCTZ, exist. Acetazolamide will have the benefit of increasing potassium excretion due to enhanced sodium and bicarbonate delivery to the distal tubule but it is an ineffective antihypertensive agent. Finally, spironolactone is likely to increase the serum potassium further and should be avoided.

Case 2
A 49-year-old Caucasian woman is referred to you for evaluation of chronic hyponatremia. Over the past 5 years, her primary care physician has noted serum sodium levels to be 129–132 meq/L on numerous measurements. The patient had no complaints and her physical examination was within normal limits. Past medical history is notable for obesity (body mass index of 31 kg/m²) and well controlled hypertension and hyperlipidemia. Of note, she remembers that her brother was also diagnosed with hyponatremia as a very young child. Medications include lisinopril 10 mg daily and simvastatin 20 mg daily. Past work-up for hyponatremia has included normal thyroid function tests, normal serum cortisol, normal renal and liver function and a normal chest radiograph. Physical examination is within normal limits. The following laboratory values are available for your review (Table 2). Laboratory work today is shown in Table 3. Furthermore, the patient’s urine osmolality was 312 mOsm/kg and urine sodium and potassium were 75 meq/L and 49 meq/L, respectively.

Question 3
Which of the following sequelae has been associated with chronic hyponatremia?

a. Increased risk of falls and bone fractures
b. Muscle and joint pain
c. Chronic abdominal pain and nausea
d. Depression
e. Increased risk of bacterial infections

The correct answer: A. The responses from fellowship program directors, fellows-in-training, and the audience are shown in Figure 4.

Case Discussion
Mild, chronic hyponatremia is a relatively common occurrence in elderly patients (prevalence in the community of approximately 7%) and it has previously been thought of as a benign condition with most patients being asymptomatic and the diagnosis occurring as an incidental finding on routine laboratory work (30,31). More recently, however, chronic hyponatremia has been associated in observational studies with both an increased incidence of falls (approximately four-fold higher than in a control population) as well as a higher bone fracture rate (approximately three-fold higher than in a control population) and higher incidence of osteoporosis (32,33). The explanations for these findings are: (1): hyponatremia is associated with significant gait and psychomotor abnormalities leading to unsteadiness (32,34), and (2) hyponatremia, through unclear mechanisms, has effects on both osteoclasts and osteoblasts, which decrease bone integrity and strength (35,36). Thus, the combination of an unsteady gait and osteoporosis explains the augmented risk of both falls and fractures in patients with chronic hyponatremia. What is not known is whether the effective correction of hyponatremia leads to a decreased risk.

To discuss the incorrect answers, hyponatremia has not been associated with muscle or joint pain, chronic abdominal pain and nausea, or an increased risk of bacterial infections. Any association of hyponatremia with depression is unclear mechanisms, has effects on both osteoclasts and osteoblasts, which decrease bone integrity and strength (35,36). Thus, the combination of an unsteady gait and osteoporosis explains the augmented risk of both falls and fractures in patients with chronic hyponatremia. What is not known is whether the effective correction of hyponatremia leads to a decreased risk.

Table 2. Case 2: Past Serum Sodium Levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum Sodium (meq/L)</th>
<th>Urine Osmolality (mOsm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2011</td>
<td>130</td>
<td>435</td>
</tr>
<tr>
<td>September 2013</td>
<td>128</td>
<td>301</td>
</tr>
<tr>
<td>August 2014</td>
<td>129</td>
<td>310</td>
</tr>
<tr>
<td>June 2015</td>
<td>127</td>
<td>201</td>
</tr>
</tbody>
</table>

Question 4
Which of the following laboratory tests would you order next for this patient?

a. Colonoscopy
b. Chest computed tomography (CT) scan
c. Serum arginine vasopressin level
d. Magnetic resonance imaging of the brain
e. Water-deprivation test

Table 3. Case 2: Laboratory Values

<table>
<thead>
<tr>
<th>Laboratory Test (Blood)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>128.0 meq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.1 meq/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>23.0 meq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>94.0 meq/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>78.0 mg/dL</td>
</tr>
</tbody>
</table>
The correct answer: C. The responses from fellowship program directors, fellows-in-training, and the audience are shown in Figure 5.

Case Discussion

In order to address this question it is important to review the facts of the case: (1) this patient has long-standing hyponatremia (>4 years) and thus has a malignancy, as the etiology is otherwise highly unlikely (therefore a colonoscopy or CT scan of the chest is unlikely to show the underlying pathology), (2) the urine osmolality values provided are all inappropriate; the normal response to a hypo-osmolar state is to excrete a dilute urine (osmolality <100 mOsm/kg) and therefore this indicates some vasopressin effect on urine-concentrating capacity, (3) the patient has a normal physical examination as well as normal renal, adrenal and thyroid function (thus brain magnetic resonance imaging and chest CT scan are unlikely to show the underlying pathology), and (4) all of the findings appear to be consistent with the syndrome of inappropriate antidiuretic hormone release (SIADH) (38). A water-deprivation test is useful in the setting of suspected diabetes insipidus and hypernatremia, and is not appropriate in the diagnosis of hyponatremia (water restriction would be a possible treatment for SIADH) (39). Thus, measurement of vasopressin (AVP) (also referred to as antidiuretic hormone) and the finding of an elevated AVP level would be consistent with the possible diagnosis of SIADH. As
noted by Robertson, in the case of SIADH, AVP is inade-quately suppressed upon return of plasma osmolality to normal levels (40). Thus, there are inappropriately high circulating levels of AVP relative to the hypo-osmolality (fall in plasma osmolality to <270 mOsm/kg and plasma sodium ions to <130 mEq/L) of body fluids (40).

It is important to note that reliable measurement of AVP is hindered by several factors. One of the most important is that over 90% of AVP is tightly bound to platelets, and AVP measurement in plasma can be confounded by the number of platelets, or incomplete removal of platelets from the specimen (41). In addition, AVP is also highly unstable in isolated plasma — even when stored at −20°C (42). An alternative measurement to AVP is that of copeptin (CTproAVP). CTproAVP is a 39-amino acid glycopeptide and a carboxy-terminal part of the precursor preprovaso-pressin protein. Activation of the hypothalamic sensing system (for example, by a rise in serum osmolality) stim-ulates CTproAVP secretion into the circulation from the posterior pituitary gland in equimolar amounts with AVP (43). Therefore CTproAVP directly reflects AVP concentration and can be used as a surrogate biomarker of AVP secretion as it is biologically more stable. CTproAVP assays are, however, yet to be widely available in the United States at this time.

Case 2 Continued

The patient is admitted to a clinical research center for further studies. The patient was given a water load of 20 ml/kg (1200 ml) and the results were documented 4 hours later, as shown in Table 4.

Question 5

Which of the following is the most likely etiology of this patient’s hyponatremia?

a. Reset osmostat
b. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

c. Psychogenic polydipsia
d. Nephrogenic syndrome of inappropriate antidiuresis
e. Empty sella syndrome

The correct answer: D. The responses from fellowship program directors, fellows-in-training, and the audience are shown in Figure 6.

Case Discussion

The kidney’s normal response to a water load is to dilute the urine (urine osmolality <100 mOsm/kg) in an effort to excrete the excess water and maintain normal serum osmolality (44). Thus, AVP levels should fall rapidly and become undetectable, and >95% of the water load is excreted within 4 hours (the majority in the first 2 hours). Finally, given the kidney’s ability to rapidly excrete the water load, the serum sodium should remain unchanged pre- and postwater load (44). In this patient, response to the water load was markedly abnormal with inappropriate retention of water, a fall in the serum sodium and remarkably undetectable AVP levels. A recently described syndrome, termed the nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is the likely diagnosis in this case. As shown in Figure 7, in the control patient who receives a
water load the urine volume rises rapidly and the urine osmolality falls. However, in the patient with NSIAD there is no ability to dilute the urine rapidly and thus urine osmolality remains relatively constant and the urine volume does not increase. Thus, water is retained and the serum sodium falls.

In earlier observations, 10%–20% of patients with presumed SIADH were noted to have undetectable AVP levels suggesting an alternative mechanism of inappropriate water handling in some patients (45). One such possible alternative mechanism was described in 2005 with the finding of two cases of 3-month-old boys with severe hyponatremia, inappropriate antidiuresis and undetectable AVP levels (46). These infants were subsequently found to have gain-of-function mutations in the AVP type 2 receptor (AVPR2) gene on the X chromosome (of note, loss-of-function mutations in the same gene lead to congenital nephrogenic diabetes insipidus).

The syndrome is characterized by several key findings: (1) most, but not all, mutations are in codon 137 changing the amino acid from arginine to either cysteine or leucine, (2) although the disorders are predominantly seen in males (as they are linked to the X chromosome), affected females might have preferential inactivation of the normal allele, (3) phenotypic variability can be seen with differences in serum sodium levels as well as in the time of onset of hyponatremia, and (4) patients appear to have SIADH but have undetectable AVP levels and vasopressin type 2 receptor antagonists (vaptans) therapy does not change urine osmolality or serum sodium (47–50). Although the initial descriptions of NSIAD were in children and infants, more recent data suggest a relatively wide range of presentations with males presenting in their 70s as well as females in their 40s, all with the same arginine to cysteine mutation at codon 137 (47). Furthermore, the range of presenting sodium values is wide and might reflect variable diet/solute intakes as well as personal levels of water intake and other determinants of the urine-concentrating mechanisms (47). The role of other modifying genes in this syndrome is not determined. Interestingly, functional polymorphisms at the arginine 137 codon of AVPR2 do not influence the serum sodium concentration at the population level (51). However, a nonsynonymous polymorphism in an element of the central tonicity-sensing mechanism in the mammalian hypothalamus (the transient receptor potential vanilloid four channel) is associated with population variations in the serum sodium (52). The possible interactions between this polymorphism and mutations in AVPR2 is not known. Therapy of patients with NSIAD focuses on fluid restriction and possibly the use of urea (to increase solute and free-water excretion) (53). In a report of 13 patients with NSIAD, this therapy was effective and well tolerated (53). The authors pointed out that fluid restriction seemed to be better tolerated than in patients with SIADH and may be due to the low AVP levels (which stimulate thirst) in NSIAD patients (53). As described above, vaptans are not effective for most cases of NSIAID but it is likely that these patients would respond to a combination of loop diuretics to dilute the urine as well as sodium supplementation. It is important to note that not all mutations in the AVPR2 lead to insensitivity to vaptans, such as with the phenylalanine to valine mutation at codon 229 (54) which causes the V2 vasopressin receptor antagonists to silence the constitutive signaling activity of the mutant receptor. Thus, identification of the specific mutation in these cases is of critical importance in determining treatment options.

Disclosures
None.


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