Answers and Explanations

Question 1
Answer B: Metformin toxicity
This patient had metformin accumulation due to chronic renal failure and inability to excrete metformin. Newer combination oral diabetes regimens containing metformin may inadvertently cause prescribing errors and complicate the diagnosis of metformin-associated lactic acidosis. While sepsis can present with many of the manifestations seen in this patient, the history of metformin use in a patient with ESRD makes it the likeliest culprit. Amiodarone toxicity is not associated with metabolic acidosis. Pyroglutamic acidosis is associated with acetaminophen use.


Question 2
Answer B: High luminal calcium antagonizing aquaporin 2 translocation to the apical plasma membrane
Hypercalcemia produces polyuria and natriuresis through a variety of mechanisms including inhibition of sodium transport in the thick ascending limb of Henle’s loop and through altered responsiveness to vasopressin in the collecting duct. The key action is apparently based on a luminal effect of calcium to antagonize the insertion of aquaporin channels into the apical membrane rather than the effect of high calcium levels in the plasma. This may explain in part the lack of an action of Familial Hypocalciuric Hypercalcemia to produce nephrogenic diabetes insipidus. In this patient, nephrogenic diabetes insipidus is the result of the actions of hypercalcemia and the marked hypercalciuria.


Question 3
Answer A: Oral antibiotic therapy
D-lactic acidosis, also referred to as D-lactate encephalopathy, is a rare neurologic syndrome that occurs in individuals with short bowel syndrome or following jejuno-ileal bypass surgery. Symptoms
typically present after the ingestion of high-carbohydrate feedings. Neurologic symptoms include altered mental status, slurred speech, and ataxia, with patients often appearing drunk. Onset of neurologic symptoms is accompanied by metabolic acidosis and elevation of plasma D-lactate concentration. Humans have the capacity to metabolize L- and D-lactate but if carbohydrate intake is concentrated over a shorter period of time, with simple, easily fermentable sugars, the rate of D-lactate metabolism may be exceeded. D-Lactic acidosis should be considered when any patient with short bowel syndrome or other malabsorptive disorder presents with neurologic symptoms consistent with the syndrome, with no other causes identified. Serum lactate by normal laboratory analysis may be elevated but is frequently normal. Because there is normally negligible D-lactate in the blood, routine blood tests are designed to only assay for L-lactate. A specific request for D-lactate is required to determine plasma D-lactate concentration. Oral antibiotic therapy can be initiated to hasten a change in the intestinal flora to one with fewer D-lactate-producing bacteria. This will allow a more rapid reintroduction of appropriate sources and amounts of carbohydrate back into the diet when recovery from the neurologic episode is complete. While infusions of L-lactate would produce an increase in bicarbonate levels as would hemodialysis, they are not tackling the underlying problem. Fomepizole would antagonize the conversion of alcohols to breakdown products but would not influence D-Lactate levels.


**Question 4**

**Answer D: Acute water intoxication**

Current evidence strongly supports that exercise-induced hyponatremia is, in large part, dilutional in nature. In the majority of athletes who develop hyponatremia, there is an increase in total body water relative to that of total body exchangeable sodium. This is primarily due to excess water ingestion during prolonged exercise. It is those individuals who are marathon novices and remain in the event for over 5 hours who are most at risk.

Question 5
Answer C: Saline infusions
The key to assessing polyuria is to assess the physical examination and the composition of the urine. In this case, the patient has no signs of volume depletion (including a low BUN level) and normal vital signs. The entire urinary osmolality is composed of electrolyte. The only way that all this can occur is if the patient is merely responding to saline infusions. There is no unaccounted osmoles in the urine so glycosuria is not present and the same holds for a urea diuresis. Answers D and E would suggest a water diuresis is the cause of polyuria but the urinary osmolarity speaks to a solute diuresis.


Question 6
Answer B: He has metabolic alkalosis and metabolic acidosis
The key finding in this case is a large anion gap with a “normal” arterial blood gas evaluation. The latter is best interpreted by the hypothesis that the patient must have had a much higher serum bicarbonate level prior to the development of a metabolic acidosis which lowered the bicarbonate level back to the normal range. Hence there are 2 concurrent acid base disorders- metabolic acidosis and metabolic alkalosis. The large anion gap of 36 mEq/L suggest that a process consumed approximately 22 mEq/L of bicarbonate with the buffering of 24 mEq/L of an organic acid introduced into the body fluids.


Question 7
Answer D: Thyroid-stimulating hormone assay
Thyrotoxic periodic paralysis is a common complication of hyperthyroidism in Asian men. Hypokalemia and muscle paralysis results from a sudden intracellular shift of potassium. Clinical features of hyperthyroidism in patients with thyrotoxic periodic paralysis may be subtle. Immediate potassium supplementation is indicated. Nonselective beta-adrenergic blockers can ameliorate and prevent recurrence of the paralytic attacks. This episodic paralysis will remit with definitive control of hyperthyroidism. The proper choice in this case is D – a TSH assay to document hyperthyroidism. Hyperaldosteronism is possible but the absence of hypertension and the severity of hypokalemia make that diagnosis less likely.
Question 8

Answer C: Suppression of ADH secretion and increased fluid delivery to the collecting duct

In an elderly patient treated with thiazide diuretics, the likeliest cause of hyponatremia is related to thiazide use. Although thiazides do not inhibit the ability to concentrate the urine, they impair diluting ability in several ways: inhibition of sodium and chloride transport at cortical diluting sites; stimulation of vasopressin release; reduction of glomerular filtration and enhanced proximal water reabsorption, which reduce delivery to the distal diluting sites; and, possibly, a direct effect on water flow in the collecting duct. Water retention caused by impaired water excretion combined with cation depletion may result in severe hyponatremia. In this case, the acute water diuresis that followed the infusion of isotonic saline suggested that vasopressin release was now suppressed. However, the clinical description suggested ongoing extracellular volume depletion which would also correct with the saline infusion. Therefore, C is the best choice. Correction of the volume depletion induced in part by the diuretic would result in increased delivery of tubular fluid from the more proximal portions of the nephron to the distal tubule and collecting duct resulting in higher urine flow rates as vasopressin secretion is also reduced.


Question 9

Answer A: Increased proximal tubular citrate reabsorption

Patients with distal renal tubular acidosis are characterized by hyperchloremic acidosis, hypocitraturia, and high urine pH. The use of carbonic anhydrase inhibitors such as acetazolamide, topiramate, and zonisamide leads to a similar picture.

Hypocitraturia is a known risk factor for kidney stone formation. By forming soluble complexes with calcium, citrate prevents crystal nucleation, aggregation and growth; therefore, the presence of citrate in the urine reduces the risk for calcium stone formation. Ingested citrate is rapidly metabolized, and plasma citrate levels vary little, so changes in filtered load do not significantly influence urinary citrate excretion. Changes in urinary citrate excretion are predominantly influenced by the rate of citrate absorption from the glomerular filtrate and metabolism by the proximal tubule cell. The former is mediated by the apical membrane cotransporter NaDC1, and the latter is mediated by both cytoplasmic and mitochondrial metabolism. Acid-base status is the most important physiological
determinant of urinary citrate excretion, by modulating the activities of NaDC1 and cytoplasmic (ATP citrate lyase) and mitochondrial (m-aconitase) enzymes involved in citrate metabolism. Following an acid load, both the transport and metabolic processes are up-regulated leading to hypocitraturia; in contradistinction, an alkaline load increases citrate excretion.

Treatment options to specifically prevent calcium phosphate stone recurrence or nephrocalcinosis progression include citrate supplementation, although the concomitant increase in urine pH may increase calcium phosphate supersaturation and partially offset the inhibition of crystallization resulting from the increased urine citrate excretion and the alkali-associated reduction in urine calcium excretion.


Question 10
Answer C: 4.5 L of free water
The correct answer may be determined using the formula on the effect of one liter of infusate of sodium containing fluid on the serum sodium concentration from Adrogue and Madias:

\[
\text{Change in serum sodium induced by one liter of fluid} = \frac{\text{Infusate sodium} - \text{Serum Sodium}}{\text{Total body water}} + 1
\]


Question 11
Answer A: 5% dextrose in water at a rate to match urine output
During the treatment of hyponatremia, circumstances may arise whereby the excretion of dilute urine increases the serum sodium concentration by much more than would be predicted by calculations, especially those that ignore the impact of induced urine output of free water. There are several settings in which this can occur but particularly following volume resuscitation in patients with excess vasopressin caused by hypovolemia or discontinuation of thiazide diuretics. Once the cause of water retention ends, a spontaneous water diuresis ensues, which may increase the plasma sodium concentration by 2 mmol/L/h or more. While there are animal studies to support the use on desmopressin in cases like the one illustrated in this question, there is little clinical data to support its use. The infusion of free water to match urine output will prevent any further falls in serum sodium due to the ongoing water diuresis.


**Question 12**

**Answer A: Plasma aldosterone to renin ratio**

Recommendations of the Endocrine Society: “We recommend case detection of primary aldosteronism be sought in higher risk groups of hypertensive patients and those with hypokalemia by determining the aldosterone-renin ratio under standard conditions and that the condition be confirmed/excluded by one of four commonly used confirmatory tests. We recommend that all patients with primary aldosteronism undergo adrenal computed tomography as the initial study in subtype testing and to exclude adrenocortical carcinoma. We recommend the presence of a unilateral form of primary aldosteronism should be established/excluded by bilateral adrenal venous sampling by an experienced radiologist and, where present, optimally treated by laparoscopic adrenalectomy. We recommend that patients with bilateral adrenal hyperplasia, or those unsuitable for surgery, optimally be treated medically by mineralocorticoid receptor antagonists.”


**Question 13**

**Answer B: The ratio of urinary sodium and urinary potassium to 24-hour urinary volume**

The most explicit model describing plasma [Na⁺] was proposed by Edelman in 1958. According to Edelman's study of 98 heterogeneous patients in steady state, the measured plasma [Na⁺] in the group can be described as a function of exchangeable Na⁺ (eNa⁺), exchangeable K⁺ (eK⁺), and total body water (TBW): For clinical purposes, the equation may be written:

\[
\text{Plasma Sodium} = \frac{\text{Total body Na} + \text{Total body K}}{\text{Total body water}}
\]

This equation has been validated in several models. Potassium must be included since it is the principle intracellular cation and a fall in cell potassium will either induce sodium entry into the cell or force water to leave the cell down its osmotic gradient. Hence, in assessing the effect of urine output on serum sodium concentration, one must assess sodium, potassium and water losses to assess the subsequent change on serum sodium, assuming intake is constant.

**Question 14**

**Answer B: Serum magnesium**

This is a case of hypomagnesemia induced by Proton Pump Inhibitor therapy leading to hypokalemia. Hypokalemia is an often-encountered condition associated with hypomagnesemia. The hypokalemia can be refractory to potassium administration and the addition of magnesium can aid in correcting potassium losses. One proposed explanation for this phenomenon involves ROMK (the renal outer medullary $K^+$ channel), which is a key player in potassium secretion from the collecting system. Potassium permeation through ROMK channels can be blocked by physiologic levels of magnesium. Hypomagnesemia abrogates the blockade of the channels and allows inappropriate renal potassium wasting.


**Question 15**

**Answer A: SPS is no more effective than a placebo at reducing serum potassium in 24 hours in hyperkalemic patients**

There is no evidence that adding sorbitol to potassium-binding resin makes it more effective in correcting hyperkalemia. Recent studies of patients with normokalemia and mild hyperkalemia and with ESRD found the serum potassium concentration rose slightly (0.4 mEq/L) on placebo and did not change during the course of 12 hours in response to a single dose of 30 g of resin in water, 30 g of resin in 60 g of sorbitol, or 60 g of sorbitol alone. As for the safety of SPS, in 2005, the FDA had received 35 adverse event reports of serious bowel injuries associated with both oral and rectal administration of the mixture, many of them fatal. Extensive transmural infarction of the colon and ileum was observed with SPS crystals adherent to the mucosa and in luminal debris.

Question 16
Answer C: Bilateral adrenal venous aldosterone level

Recommendations of the Endocrine Society: “We recommend case detection of primary aldosteronism be sought in higher risk groups of hypertensive patients and those with hypokalemia by determining the aldosterone-renin ratio under standard conditions and that the condition be confirmed/excluded by one of four commonly used confirmatory tests. We recommend that all patients with primary aldosteronism undergo adrenal computed tomography as the initial study in subtype testing and to exclude adrenocortical carcinoma. We recommend the presence of a unilateral form of primary aldosteronism should be established/excluded by bilateral adrenal venous sampling by an experienced radiologist and, where present, optimally treated by laparoscopic adrenalectomy. We recommend that patients with bilateral adrenal hyperplasia, or those unsuitable for surgery, optimally be treated medically by mineralocorticoid receptor antagonists.”


Question 17
Answer A: The patient has Bartter’s syndrome

Bartter’s syndrome hallmark is the presence of hypokalemia between 1.5 and 3.2 mEq/L. Hypochloremia and metabolic alkalosis are almost constant, but occasionally a patient may suffer metabolic acidosis. Hyperuricemia due to volume contraction is found in half the patients, but hypomagnesemia is observed less frequently. In urine, there is salt-wasting and increased fractional excretion of K⁺, Na⁺, and Cl⁻, and normal or high urinary Ca excretion. The high calcium excretion has been noted as a key finding in Bartter’s syndrome as helping to localize the cellular defect to the thick ascending limb of Henle’s loop. In surreptitious vomiting, urine potassium is increased but urinary calcium is typically low. In laxative abuse, urinary potassium is reduced to very low values as serum potassium is reduced. Gitelman’s syndrome resembles Bartter’s syndrome in inducing hypokalemia and alkalosis but urinary calcium is low as distal nephron calcium transport is enhanced in this condition.

Question 18

Answer B: Liddle's syndrome

Liddle's syndrome is characterized by high urinary potassium excretion and low urinary sodium excretion producing hypokalemia and volume expansion and causing hypertension and suppressing aldosterone excretion. Genetic analysis of patients with Liddle's syndrome identified mutations in the ENaC [beta] or [gamma] subunits of the epithelial sodium channel in the distal nephron. The disruption of the protein structure of the epithelial sodium channel in Liddle's syndrome leads to a retention of active epithelial sodium channel at the cell surface causing increased sodium absorption in the distal nephron.


Question 19

Answer A: Measure plasma potassium

Pseudohyperkalemia is defined as a false elevation in serum or plasma potassium levels above the upper limit of the age-specific reference interval caused by potassium movement out of cells. Mechanical trauma is the commonest cause, but disorders such as familial pseudohyperkalemia also cause extracellular movement of potassium. It is a recognized phenomenon in hematological disorders such as hereditary spherocytosis, thrombocytosis and other myeloproliferative disorders and chronic lymphocytic leukemia. Pseudohyperkalemia is clearly related to the clotting process. It can be prevented by anticoagulation with heparin, but other anticoagulants, citrate and EDTA have a similar effect.


Question 20

Answer D: Pyroglutamic acidosis

A rare cause of high anion gap acidosis is 5-oxoproline (pyroglutamic acid), an organic acid intermediate of the gamma-glutamyl cycle. Acetaminophen and several other drugs have been implicated in the development of transient 5-oxoprolinemia in adults. Acetaminophen reduces intracellular glutathione levels, which relieves feedback inhibition of y-glutamylcysteine synthetase.
This causes accumulation of γ-glutamylcysteine, which is metabolized to 5-oxoproline by γ-glutamylcyclotransferase. The key in this case is awareness of the relationship between acetaminophen ingestion and metabolic acidosis. Toluene may induce renal tubular acidosis and hypokalemia. Paraldehyde may induce metabolic acidosis with prolonged use but is much more unlikely than acetaminophen induced pyroglutamic acidosis in this case.


**Question 21**

**Answer B: Urinary sodium, 40 mEq/L; urinary potassium, 5 mEq/L; urinary volume 2 L**

The most explicit model describing plasma [Na⁺] was proposed by Edelman in 1958. According to Edelman's study of 98 heterogeneous patients in steady state, the measured plasma [Na⁺] in the group can be described as a function of exchangeable Na⁺ (eNa⁺), exchangeable K⁺ (eK⁺), and total body water (TBW): For clinical purposes, the equation may be written:

\[
\text{Plasma Sodium} = \text{Total body Na} + \frac{\text{Total body K}}{\text{Total body water}}
\]

This equation has been validated in several models. Potassium must be included since it is the principle intracellular cation and a fall in cell potassium will either induce sodium entry into the cell or force water to leave the cell down its osmotic gradient. Hence, in assessing the effect of urine output on serum sodium concentration, one must assess sodium, potassium and water losses to assess the subsequent change on serum sodium, assuming intake is constant.

In this case, only the character of the urine in answer B, by increasing excretion of free water in a urine that is dilute with respect to total Na and K content, can lead to a rise in serum sodium. All of the other options contain too much total electrolytes to allow serum sodium to rise.

Question 22

Answer D: Magnetic resonance imaging of the brain

The development of hyponatremia during a period of poor fluid intake and with a urine osmolarity less than 100 mOsm/L suggests diabetes insipidus and likely central diabetes insipidus given the very low urinary osmolality. Fluid deprivation would be dangerous and unnecessary in this case as there is simultaneous low urinary osmolarity and hyponatremia. While plasma cortisol and TSH assay could show multiple endocrine abnormalities associated with pituitary insufficiency, MRI would be the most direct proof of potential damage to the posterior pituitary gland secondary to metastatic breast cancer as was the case here.


Question 23

Answer A: Interference with normal transport through the epithelial sodium channel in the collecting duct

Trimethoprim-sulfamethoxazole is a commonly prescribed antimicrobial agent. Twenty-five years after its introduction into clinical practice, an unrecognized and potentially lethal adverse reaction associated with trimethoprim-sulfamethoxazole therapy, hyperkalemia, was described. Both "high-dose" and "standard-dose" trimethoprim-sulfamethoxazole have been associated with this electrolyte disorder. Recognition of this potassium disturbance led to the subsequent description of the mechanism by which trimethoprim-sulfamethoxazole induced hyperkalemia. Trimethoprim was found to act like the potassium-sparing diuretic amiloride and reduce renal potassium excretion. Its action is through binding to and blocking transport associated with the epithelial sodium channel (ENaC) in the distal nephron. Hence, trimethoprim is in fact a potassium-sparing diuretic like amiloride and causes hyperkalemia in high-risk patients.


Question 24

Answer A: Treatment with dexamethasone

The strong family history of early and severe hypertension combined with an electrolyte pattern suggestive of mineralocorticoid effect suggests the possibility of a hereditary form of hyperaldosteronism. Glucocorticoid-remediable aldosteronism (GRA) is a hereditary form of primary hyperaldosteronism and the most common monogenic cause of hypertension. A chimeric gene...
duplication leads to ectopic aldosterone synthase activity in the cortisol-producing zona fasciculata of the adrenal cortex, under the regulation of adrenocorticotropicin (ACTH). Hypertension typically develops in childhood, and may be refractory to standard therapies. Hypokalemia is typically mild. Glucocorticoid supression of ACTH is the mainstay of treatment; alternative treatments include mineralocorticoid receptor antagonists. Of the choices presented, A represents the least invasive yet most likely to provide the diagnosis.


**Question 25**

**Answer B: Sjögren’s syndrome**

Sjögren’s syndrome is a type of autoimmune disease with multiple organs involved apart from exocrine glands. Renal involvement is one of the most common manifestations of Sjögren’s syndrome and is mainly manifested as tubular disorders, especially as dRTA. In Ren et al. series, 93 of 130 patients manifested distal RTA. The diagnosis in this case may be made based on the clinical findings of painful dry eyes and the findings of a high urine pH in the face of severe hypobicarbonatemia along with a narrow urinary anion gap (indicating minimal ammonium excretion). Diuretic use would provoke hypokalemia but not high urinary pH. Laxative abuse would not be associated with urinary potassium wasting in the face of hypokalemia.


**Question 26**

**Answer B: Proximal renal tubular acidosis (RTA)**

This patient manifests hypokalemia, hypobicarbonatemia and glycosuria raising the possibility of Fanconi’s syndrome, particularly with a history of exposure to a drug known to cause Fanconi syndrome, ifosfamide. The acquired causes of Fanconi syndromes with proximal RTA include amyloidosis, multiple myeloma, paroxysmal nocturnal hemoglobinuria, renal transplantation, antiretroviral drugs, ifosfamide, cadmium and lead toxicity. Laxative abuse would not be associated with renal potassium wasting and distal RTA would not typically be associated with glycosuria or with an acid urine pH. Type IV RTA is associated with hyperkalemia.

Question 27

Answer A: Ethylene glycol intoxication
This case demonstrates a clear example of apparently acute severe metabolic acidosis with a large anion gap and mental obtundation. The differential diagnosis must include ingestion of a toxic alcohol. The hallmark of ethylene glycol ingestion is the finding of “envelope” shaped calcium oxalate dihydrate crystals in the urine. However, on occasion, the monohydrate crystals may be found. These crystals (Figure 1) have a “brush” shaped configuration. Early intervention with fomepizole and dialysis is typically required. Methanol poisoning is possible and presents with a similar electrolyte pattern but not crystalluria, Toluene may produce brush like crystals but not typical acute metabolic acidosis. Isopropyl alcohol does not induce acidosis.

- Luqman A, Stanifer J, Asif Siddiqui OM, Naseer A, Wall BM:

Question 28

Answer B: Serum sodium no higher than 120 mEq/L by 24 hours after initiation of therapy
According to Sterns et al, A 4- to 6-mmol/L increase in serum sodium concentration is adequate in the most seriously ill patients and this is best achieved with bolus infusions of 3% saline. Virtually all investigators now agree that overcorrection of hyponatremia (which we define as 10 mmol/L in 24 hours, 18 mmol/L in 48 hours, and 20 mmol/L in 72 hours) risks iatrogenic brain damage. Appropriate therapy should keep the patient safe from serious complications of hyponatremia while staying well clear of correction rates that risk iatrogenic injury. Accordingly, Sterns et al as well as other experts suggest therapeutic goals of 6 to 8 mmol/L in 24 hours, Answer B is the only answer that fulfills this goal.

Question 29
Answer C: Water deprivation study
The finding of mild hyponatremia with a high urine output of substantially dilute urine suggests increased water intake and hypotonicity as the cause of ADH suppression. Water deprivation study would prove the diagnosis. Desmopressin infusion would be dangerous given the relatively low serum sodium level to begin with.


Question 30
Answer C: Mechanical ventilation
This patient’s clinical picture is most consistent with distal RTA with high urine pH, no glycosuria, and severe hypokalemic metabolic acidosis with a normal anion gap. Patients with severe hypokalemia are at risk of cardiac arrhythmias and ventilatory failure due to muscle weakness. While the patient does need to receive bicarbonate infusions and potassium infusions, initial therapy should consist of airway protection as any bicarbonate infusion could further depress the serum potassium level and potassium administration may take several hours to restore muscle strength and respiratory failure could supervene.