Answers and Explanations

## Question 1

**Educational objective: Manage diuretic breaking.**

**Answer D: Increase furosemide to 40 mg twice daily**

This woman initially had a diuretic response to furosemide, 40 mg daily, associated with a loss of 4 kg. She now seems to have reached a new equilibrium, maintaining the 4 kg weight loss, but with no additional diuresis. This "diuretic-braking" phenomenon is due to activation of the renin-angiotensin-aldosterone system in response to hypovolemia and consequent renal sodium avidity induced by the initial diuresis. An increase in the furosemide to 40 mg twice daily is the best initial management strategy; option D is correct. Addition of a second dose of furosemide later in the day results in the excretion of sodium ingested later in the day, thereby facilitating further sodium excretion. The rise in the serum creatinine level is most likely due to diuresis and relative volume depletion. It would not be appropriate to discontinue furosemide (option A) because this woman continues to have significant congestive symptoms. The 20% rise in the serum creatinine is acceptable because effective treatment of congestion is associated with improved outcomes despite initial worsening of kidney function. Similarly, lisinopril (option B) should be continued because ACE inhibition decreases afterload and improves cardiac output. In addition, ACE inhibitor therapy is associated with decreased mortality in patients with systolic heart failure. An increase in the morning dose of furosemide to 80 mg (option C) would be less effective because it would not address sodium retention that occurs later in the day. Moreover, this woman has already demonstrated a diuretic response to a dose of 40 mg. Therefore; an increase in the furosemide dose to 80 mg is not necessary.

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- Verbrugge FH, Mullens W, Tang WHW: Management of Cardio-Renal Syndrome and Diuretic Resistance. *Curr Treat Options Cardio Med* 18: 11, 2016
- Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP: Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 122: 265–72, 2010
- Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH: Timing of Hemoconcentration During Treatment of Acute Decompensated Heart Failure and Subsequent Survival; Importance of Sustained Decongestion 6;62(6): 516-24, 2013

**Question 2**

**Educational objective: Treat SIADH**

**Answer D: Furosemide at 40 mg/d plus sodium chloride tablets at 1 g three times daily**

This man has severe SIADH because he has clinically euvolemic hypotonic hyponatremia with a level of urine osmolality that is greater than maximally dilute (*i.e.*, > 100 mOsm/kg) and a urine sodium >40 mEq/L. Furosemide interferes with the generation of the medullary osmotic gradient, thereby decreasing urine osmolality, and increasing free water clearance. Addition of sodium chloride tablets (and, if needed, potassium chloride) would replace diuretic-induced sodium chloride losses and prevent superimposed hypovolemia. Therefore, option D is correct. The sum of the urine sodium and potassium levels, 140 mEq/L, is greater than the serum sodium level of 125 mEq/L. Hence, the electrolyte free water clearance is negative. Electrolyte free water excretion ($C_eH_2O$) is calculated by the following equation.

$C_eH_2O = V (1 - [U_{Na} + U_K]/P_{Na})$ where

$V$ = daily urine volume

$U_{Na}$ = urine sodium concentration

$U_K$ = urine potassium concentration

$P_{Na}$ = plasma sodium concentration

When the ratio of $[U_{Na} + U_K]/P_{Na} >1$, as it is in this case, the electrolyte free water clearance is negative. Therefore, this man is retaining electrolyte free water that would tend to further reduce the serum sodium level. Free water restriction is predictably ineffective when the electrolyte free water clearance is negative. Therefore, options A and B are incorrect. 3% saline should only be used in patients with moderate to severe symptomatic hyponatremia. Hence, it would not be appropriate to use 3% saline (option C) in this man with chronic asymptomatic hyponatremia.

- Greenberg A, Verbalis JG, Amin AN, Burst VR, Chiodo III JA, Chiong JR, Dasta JF, Friend KE, Hauptman PJ, Peri A, Sigal SH: Current treatment practice and outcomes. Report of the hyponatremia registry. *Kidney Int* 88 167–177, 2015
- Dasta J, Waikar SS, Xie L, Boklage S: Patterns of treatment and correction of hyponatremia in intensive care unit patients. *J Critical Care* 30:1072-1079, 2015
- Decaux G: Treatment of the Syndrome of Inappropriate Secretion of Antidiuretic Hormone by Long Loop Diuretics. *Nephron* 35:82–88, 1983

**Question 3**

**Educational objective: Manage symptomatic hyponatremia.**

**Answer B: 3% saline to increase SNa+ 4–6 mEq/L**

This patient has hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) with moderate symptoms of confusion and agitation that warrant emergency treatment with

3% saline. Symptoms result from increased neuronal cell volume. Moderate symptoms may include lethargy, headache, nausea, vomiting, and confusion. More severe manifestations are seizures, coma and transtentorial herniation. The goal of treatment is to quickly raise serum sodium by 4-6 mEq/L to reverse cerebral edema and improve cognition. A 100 ml bolus of 3% saline is the most reliable and rapid means to achieve this goal. While chlorthalidone should be discontinued, this alone or in conjunction with fluid restriction will not raise the serum sodium level rapidly enough to reverse cerebral edema; therefore, option A is incorrect. The response to tolvaptan is unpredictable and may exceed or fall short of recommended treatment targets; hence, option C is incorrect. To note, tolvaptan is only approved for the treatment of asymptomatic euvolemic and hypervolemic hyponatremia. Although a combination of intravenous furosemide plus sodium and potassium replacement (option D) could be used, the rate of rise in the serum sodium level would be insufficient.

- Greenberg A, Verbalis JG, Amin AN, Burst VR, Chiodo III JA, Chiong JR, Dasta JF, Friend KE, Hauptman PJ, Peri A, Sigal SH: Current treatment practice and outcomes. Report of the hyponatremia registry. *Kidney Int* 88, 167–177, 2015
- Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al: Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 126(10 Suppl 1): S1–S42, 2013
- Sterns R: Severe symptomatic hyponatremia; treatment and outcome. *Ann Intern Med* 107:656-664, 1987

**Question 4**
**Educational objective: Identify a risk factor for exercise-induced hyponatremia**
**Answer C: Weight gain >3 kg after exercise**
Exercise-associated hyponatremia is primarily due to water gain and secondarily due to sodium chloride loss. The majority of individuals who develop exercise-associated hyponatremia gain weight during exercise as a result of excessive water intake and retention; therefore, option C is correct. While urinary indices (options A, B, and D) would shed light on the mechanism of water gain (*e.g.*, a high urine osmolality would indicate a high ADH state that is usually observed in these individuals), the final outcome is due to net water gain that is reflected in an increase in weight.

- Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, Duncan CN, Olson DP, Salerno AE, Newburger JW, Greenes DS: Hyponatremia among runners in the Boston Marathon. *N Engl J Med* 352: 1550–1556, 2005
- Mayer CU, Treff G, Fenske WK, Blouin K, Steinacker JM, Allolio B: High Incidence of Hyponatremia in Rowers during a Four-Week Training Camp. *Am J Med* 128(10):1144-51, 2015
- Hew-Butler T, Rosner MH, Fowkes-Godek S, Dugas JP, Hoffman MD, Lewis DP, MD, Maughan KRJ, Miller KC, Montain, SJ, Rehrer NJ, Roberts WO, Rogers IR, Siegel AJ, Stuempfle KJ,

Winger JM, Verbalis JG: Statement of the Third International Exercise-Associated Hyponatremia Consensus Development Conference, Carlsbad, California, 2015. *Clin J Sport Med* 25: 303–320, 2015

**Question 5**
**Educational objective: Manage desmopressin-induced hyponatremia**
**Answer C: Continue desmopressin, decreasing fluid intake in response to thirst only**

This patient has _asymptomatic_ hyponatremia secondary to desmopressin prescribed for refractory nocturnal polyuria and enuresis. Desmopressin-induced hyponatremia is usually mild and responds well to fluid restriction. Thirst should be used to guide fluid intake. Hence, option C is correct. Although discontinuation of desmopressin (option A) would likely normalize the serum sodium concentration, this intervention would not address his initial complaint of enuresis. Discontinuation of intranasal desmopressin would be appropriate if he had _symptomatic_ hyponatremia. If the rate of rise on the serum sodium was insufficient in a _symptomatic patient_ (unlike this patient), 3% saline (option B) could be added, with consideration for concurrent administration of subcutaneous desmopressin to prevent excessively rapid correction of the hyponatremia. In most cases of desmopressin-induced hyponatremia, however, discontinuation of desmopressin alone results in a prompt water diuresis. Increased dietary sodium (option D) would facilitate solute-mediated water excretion. However, this option is less attractive because it could potentially exacerbate his heart failure.

- Choi EY, Park JS, Kim YT, Park SY, Kim GH: The risk of hyponatremia with desmopressin use for nocturnal polyuria. *Am J Nephrol* 41:183–190, 2015
- Song M, Hong BS, Chun JY, Han JY, Choo MS: Safety and efficacy of desmopressin for the treatment of nocturia in elderly patients: a cohort study. *Int Urol Nephrol* 46:1495–1499, 2014
- Achinger SG, Arieff AI, Kalantar-Zadeh K, Ayus JC: Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: a case series. *Nephrol Dial Transplant* 29: 2310–2315, 2014

**Question 6**
**Educational objective: Manage overly rapid correction of hyponatremia**
**Answer B: Desmopressin at 4 μg subcutaneously plus intravenous 5% dextrose in water (D5W) to achieve a serum sodium of 118–122 mEq/L**

This patient has pronounced desmopressin-induced hyponatremia. He does not have moderate or severe symptoms such as nausea, headache, confusion, or seizures, indicating that the hyponatremia is relatively chronic in nature. He is now undergoing a brisk water diuresis after discontinuation of desmopressin. The rate of rise is sodium (8 mEq/L in 4 hours) is excessively rapid and should be rapidly reversed. Restarting desmopressin alone would only prevent further increases, but would not

decrease the serum sodium concentration; hence, option A is incorrect. In addition to giving desmopressin, intravenous $D_5W$ should be administered in order to decrease and maintain the serum level in the 118 mEq/L to 122 mEq/L range over the first 24 hours. Therefore, option B is correct. Option C is incorrect because 3% saline is indicated for symptomatic hyponatremia; this man is asymptomatic. Furthermore, 3% saline would worsen the overly rapid correction of the hyponatremia. Infusion of $D_5W$ at a rate of 250 ml/h would not sufficiently lower the serum sodium level in this patient with a urine flow rate of 500 ml/h. Hence, option D is incorrect.

- Achinger SG, Arieff AI, Kalantar-Zadeh K, Ayus JC: Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: a case series. *Nephrol Dial Transplant* 29: 2310–2315, 2014
- Sood L, Sterns RH, Hix JK, Silver SM, Chen L: Hypertonic saline and desmopressin: A simple strategy for safe correction of severe hyponatremia. *Am J Kidney Dis* 61: 571–578, 2013
- Rafat C, Schortgen F, Gaudry S, Bertrand F, Miguel-Montanes R, Labbe V, Ricard JD, Hajage D, Dreyfuss D: Use of desmopressin acetate in severe hyponatremia in the intensive care unit. *Clin J Am Soc Nephrol* 9: 229–237, 2014

**Question 7**
**Educational objective: Prevent metformin associated lactic acidosis**
**Answer A: Discontinue metformin 2–3 days before CA**

This patient has stage 3b: A3 chronic kidney disease secondary to diabetic kidney disease and heart failure. As a result, she is at increased risk for the development of contrast-induced nephropathy (CIN). In patients at increased risk for contrast-induced nephropathy with decreased renal function, it is advisable to discontinue metformin two to three days before the procedure because of the risk of metformin-associated lactic acidosis (MALA). Therefore, option A is correct and option C is incorrect. Kidney function should be assessed daily for the two days following contrast administration, with resumption of metformin only after confirming stability of kidney function. There is insufficient evidence to make firm treatment recommendations regarding ACE inhibitor or angiotensin receptor blocker therapy in high-risk patients undergoing coronary angiography. Therefore, option B is incorrect. Administration of furosemide or mannitol prior to contrast administration is not recommended. However, there is no evidence that continuation of chronic diuretic therapy, particularly in patients with hypervolemia, is disadvantageous. Therefore, option D is less attractive.

- Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK: Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 312(24):2668-2675, 2014
- http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm
- Vecchio S, Giampreti A, Petrolini VM, Lonati D, Protti A, Papa P, Rognoni C, Valli A, Roccho L, Rolandi L, Manzo L, Locatelli CA. Metformin accumulation: Lactic acidosis and high

plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. *Clin Toxicol* 52, 129–135, 2014

**Question 8**

**Educational objective: Manage metabolic alkalosis**

**Answer A: Discontinue furosemide and begin intravenous 0.9% saline at 125 ml/h**

This man has evidence of hypovolemia resulting in metabolic alkalosis that is superimposed on chronic respiratory acidosis. Correction of the metabolic alkalosis will require correction of the hypovolemia and hypokalemia; therefore, option A is correct. Acetazolamide would improve alkalemia by causing increased renal bicarbonate excretion, but would worsen this man's hypovolemia and hypokalemia. Therefore, option B is less attractive. Spironolactone would ameliorate the hypokalemic metabolic alkalosis over time, but would worsen this man's hypovolemia; hence, option C is incorrect. Ammonium chloride is reserved for severe metabolic alkalosis that cannot be ameliorated by correcting the underlying cause; hence, option D is incorrect.

- Galla J: Metabolic alkalosis. *J Am Soc Nephrol* 11: 369 –375, 2000
- Fontana V, Santinelli S, Internullo M, Marinelli P, Sardo L, Alessandrini G, Borgognoni L, Ferrazza AM, Bonini M, Palange P: Effect of acetazolamide on post-NIV metabolic alkalosis in acute exacerbated COPD patients. *Eur Rev Med Pharmacol Sci* 20: 37-43, 2016


**Question 9**

**Educational objective: Manage polyuria**

**Answer D: Decrease dietary sodium intake to 2–3 g/d**

This patient has lithium-induced nephrogenic diabetes insipidus (DI), but has persistent polyuria despite therapy with hydrochlorothiazide. In diabetes insipidus, thiazide diuretics decrease urine volume by causing a mild decrease in the extracellular fluid volume that causes increased proximal tubular reabsorption of the glomerular filtrate. Unlike loop diuretics, thiazide diuretics are the preferred class of diuretics for the treatment of nephrogenic DI because they do not interfere with the generation of the medullary osmotic gradient. Thiazides diuretics are less effective when dietary solute intake remains high. This patient has a daily solute output of >900 milli-osmoles. The daily sodium excretion indicates that he is consuming approximately 280 mEq (70 mEq/L × 4 L) or about 6.4 g of sodium per day. His total daily solute intake is 940 mmol per day (240 mOsm/kg × 4 L), with a large contribution from sodium and accompanying anions. The relative contribution of solute and free water clearance to the urine volume can be calculated from the following equation.

Urine Volume (V) = Cosm + $CH_2O$, where

Cosm = osmolar clearance = V × Uosm /Posm

$CH_2O$ = free water clearance = V × (1 - Uosm /Posm)

In this case,

4.0 L (urine volume) = 4.0 L (0.8) + 4 L (0.2)

4.0 L (urine volume) = 3.2 L (osmolar clearance) + 0.8 L (free water clearance)

The relatively high osmolar clearance indicates that the polyuria is primarily due to a solute diuresis. Therefore, restriction of dietary sodium (option D) is the next best step in the management of this man's polyuria. Increasing hydrochlorothiazide (option A), or addition of amiloride (option B) will not be effective without a decrease in solute intake. Addition of desmopressin (option C) is unlikely to significantly impact the urine volume because the polyuria is primarily due to increased solute intake rather than impairment in urinary concentration. Furthermore, desmopressin has limited efficacy in the treatment of nephrogenic DI.

- Grünfeld JP, Rossier BC: Lithium nephrotoxicity revisited. *Nat Rev Nephrol* 5: 270–276, 2009
- Alsady M, Baumgarten R, Deen PM, de Groot T. Lithium in the Kidney: Friend and Foe? *J Am Soc Nephrol* 27: 1587-95, 2015
- Christensen BM, Zuber AM, Loffing J, Stehle JC, Deen PM, Rossier BC, Hummler E: alpha ENaC-mediated lithium absorption promotes nephrogenic diabetes insipidus. *J Am Soc Nephrol* 22: 253–261, 2011

**Question 10**

**Educational objective: Manage hypernatremia**

**Answer A: 4.0 L**

The amount of water required to correct the serum sodium (SNa) to 145 mEq/L can be calculated by the following equation.

Volume of water to correct SNa to 145 mEq/L = free water deficit (to achieve SNa of 145 mEq/L) + electrolyte free water clearance + insensible water losses

The following equation is used to calculate the free water deficit.

Free water deficit = Total body water $\times$ ([$P_{Na}$/Target SNa] – 1)

The total body water in this patient is 60 L X 0.60 = 36 L.

Therefore, the free water deficit = 36 L $\times$ ([155/145] – 1) = 2.5 L

Calculation of the electrolyte free water clearance is required to account for ongoing urinary losses of electrolyte free water.

$V \times [1 – (U_{Na} + U_K/ P_{Na})]$ where

V = urine flow rate or urine volume per day

$U_{Na}$ = urine sodium concentration

$U_K$ = urine potassium concentration

$P_{Na}$ = plasma sodium concentration

Electrolyte free water clearance = 2 L $\times$ [1 - (60 + 40/155)] = 0.7 L

In average sized adults, insensible water losses average 0.8 liters per day in the absence of fever or increased minute ventilation. Therefore, the amount of water required to correct this patient's SNa to 145 mEq/L over the next 24 hours is 2.5 L + 0.7 L + 0.8 L = 4.0 L. Hence. Option A is correct.

- Sterns RH: Disorders of Plasma Sodium — Causes, Consequences, and Correction. *N Engl J Med* 372: 55-65, 2015
- Hoorn EJ, Betjes MG, Weigel J, Zietse R: Hypernatraemia in critically ill patients: too little water and too much salt. *Nephrol Dial Transplant* 23: 1562–8, 2008

**Question 11**

**Educational objective: Cite the pathogenesis of exercise-associated hyponatremia**

**Answer A: Excessive water intake and retention**

Excessive water intake and retention of ingested fluid are the most important factors in the pathogenesis of exercise-induced hyponatremia; option A is correct. Exercise-induced hyponatremia is more common in individuals with a low BMI who require a longer amount of time to complete the race. Such individuals are more likely to consume proportionately larger volumes of water during a marathon. Increased arginine vasopressin levels are also increased triggered by muscular pain decreasing the capacity of the kidney to excrete free water. Water may be transiently sequestered in the gastrointestinal tract in marathon runners. This may result in further decreases in the serum sodium level after completion of the race. However, it is the ingestion and retention of water that ultimately causes exercise-induced hyponatremia. Sodium chloride losses in sweat are hypotonic and cause hypernatremia. Hypovolemic hyponatremia may ensue when there is continued water intake after onset of hypovolemia and nonosmotic release of arginine vasopressin. This patient does not have evidence of hypovolemia on physical examination; hence, option C is less attractive. As noted above, most patients with exercise-induced hyponatremia gain weight because of water ingestion and retention. As a result, both the intracellular and extracellular fluid volumes are increased at a ratio of 2:1. Therefore, option D is incorrect.

- Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, Duncan CN, Olson DP, Salerno AE, Newburger JW, Greenes DS: Hyponatremia among runners in the Boston Marathon. *N Engl J Med* 352: 1550–1556, 2005
- Lara B, Salinero JJ, Areces F, Ruiz-Vicente D, Gallo-Salazar C, Abi J: Sweat sodium loss influences serum sodium concentration in a marathon. *Scand J Med Sci Sports* 27(2): 152-160, 2017
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- van Nieuwenhoven MA, Vriens BE, Brummer RJ, Brouns F:  Effect of dehydration on gastrointestinal function at rest and during exercise in humans. *Eur J Appl Physiol* 83: 578-584, 2000

**Question 12**

**Educational objective: Manage metformin associated lactic acidosis**

**Answer D: Observation of clinical status after correction of hypovolemia**

This woman with type 2 diabetes mellitus managed with metformin now has prerenal azotemia, lactic acidosis, and hypovolemia. Although the lactic acidosis could be the result of decreased organ perfusion, metformin could be playing a role in the pathogenesis of this patient's acidosis. This woman is alert and has mild lactic acidosis that likely will improve with correction of the hypovolemia and prerenal azotemia. Therefore, volume expansion with isotonic crystalloid with observation of her clinical status after correction of hypovolemia is the best initial management strategy; therefore, option D is correct. The clinical findings, not serum levels, should guide treatment of metformin toxicity], the results of which are usually not immediately available; hence, option A is incorrect. Bicarbonate therapy is recommended when the arterial pH is <7.1. Renal replacement therapy is usually reserved for patients with severe lactic acidosis (arterial lactate levels >20 mmol/L; arterial pH ≤7.0), particularly when there is impaired consciousness, shock, or failure of standard supportive measures. Hemodialysis is favored over continuous renal replacement therapy in the absence of hemodynamic compromise. Options B and C are incorrect because this woman has relatively mild lactic acidosis and prerenal azotemia that will likely improve with volume expansion.

- Kraut JA, Madias NE: Lactic acidosis. *N Engl J Med* 371:2309-19, 2014
- Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK: Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 312(24):2668-2675, 2014
- http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm
- Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, Hoffman RS, Nolin TD, Ghannoum M, on behalf of the Extracorporeal Treatments in Poisoning Workgroup: Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. *Critical Care Med* 43: 1716-1730, 2015

**Question 13**

**Educational objective: Distinguish between the pharmacokinetic properties of furosemide and torsemide**

**Answer A: Torsemide has increased bioavailability and a longer half-life**

Torsemide has higher bioavailability (80-100%) compared to furosemide (10-100%). The elimination half-life for torsemide is three to six hours, compared to one-half to two hours for furosemide. Therefore, option A is correct. Similar to furosemide, torsemide inhibits the activity of the sodium-potassium-2-chloride transporter (NKCC2) in the thick ascending limb of the loop of Henle. It does not impede proximal tubular reabsorption of sodium or inhibit the epithelial sodium channel in the collecting

duct. Hence, options B and D are incorrect. Torsemide is less kaliuretic compared to furosemide. This is thought to be due an inhibitory effect on aldosterone secretion rather than direct blockade of the epithelial sodium channel in the collecting duct. Hence, option C is incorrect.

- Brater DC: Diuretic therapy. *New Engl J Med* 339(6): 387-95, 1998
- Knauf H, Mutschler E, Velazquez H, Giebusch G: Torsemide significantly reduces thiazide-induced potassium and magnesium loss despite supra-additive natriuresis. *Eur J Clin Pharmacol* 65:465–472, 2009
- Goodfriend TL, Ball DL, Oelkers W, Bähr V: Torsemide inhibits aldosterone secretion in vitro. *Life Sci* 63: PL45-50, 1996

## Question 14

**Educational objective: Manage SIADH**

**Answer B: 1.8 L**

The electrolyte free water clearance approximates the amount of fluid she can drink that would not result in a lowering of the serum sodium level. The electrolyte free water clearance is calculated by the following equation.

$V \times [1 - (U_{Na} + U_K / P_{Na})]$ where

$V$ = urine flow rate or urine volume per day

$U_{Na}$ = urine sodium concentration

$U_K$ = urine potassium concentration

$P_{Na}$ = plasma sodium concentration

In this case, electrolyte free water clearance = 2 L $\times$ [1 - (40 + 22/128)] = 1.0 L. Taking into account 0.8 L of insensible losses of free water per day, intake of >1.8 L would result in a fall in the serum sodium level. Thus, the correct answer is option B.

- Ellison DH, Berl T: Clinical practice: the syndrome of inappropriate antidiuresis. *N Engl J Med* 356: 2064 –2072, 2007

## Question 15

**Educational objective: Diagnose a mixed acid-base disturbance**

**Answer D: Respiratory acidosis, metabolic alkalosis, and metabolic acidosis**

The increased arterial pH, $P_aCO_2$, and total $CO_2$ ($\approx$ serum bicarbonate level) indicate that the predominant disorder is metabolic alkalosis. With normal respiratory compensation, the $P_aCO_2$ would be expected to rise about 0.7 mmHg for every 1 mmol/L increase in the total $CO_2$. Therefore, the $P_aCO_2$ should be approximately 48 mmHg in simple metabolic alkalosis with normal respiratory compensation. In this case, the measured $P_aCO_2$ exceeds the expected level, indicating concurrent respiratory acidosis. Finally, the serum anion gap is elevated at 20 mEq/L, indicating presence of unmeasured

anions and a component of increased anion gap metabolic acidosis. The presence of this triple acid-base disorder makes sense in the context of this patient's presentation. The metabolic alkalosis can be ascribed to the vomiting, hypovolemia, potassium depletion, and furosemide therapy. The history of severe obstructive lung disease suggests that there most likely is a component of chronic respiratory acidosis. A component of acute on chronic respiratory acidosis related to pneumonia is also possible. In the context of a mixed acid-base order and no reference baseline arterial blood gases, it is difficult to discern the relative contribution of acute versus chronic respiratory acidosis. The increased anion gap metabolic acidosis most likely is due to organ hypoperfusion, sepsis, and type A lactic acidosis. Therefore, option D is the best answer.

- Adrogué HJ, Madias NE: Assessing Acid-Base Status: Physiologic Versus Physicochemical Approach. *Am J Kidney Dis* 68(5): 793-802, 2016
- Adrogué HJ, Madias NE: Secondary responses to altered acid-base status: the rules of engagement. *J Am Soc Nephrol* 21: 920-923, 2010
- Berend K, de Vries AP, Gans RO: Physiological approach to assessment of acid-base disturbances. *N Engl J Med* 371: 1434-1445, 2014

**Question 16**
**Educational objective: Diagnose Bartter syndrome**
**Answer C: Bartter syndrome**

The constellation of a low to normal blood pressure, hypokalemic metabolic alkalosis, elevated urinary sodium, potassium, calcium, and chloride levels, increased plasma renin activity/plasma aldosterone is most consistent with a diagnosis of Bartter syndrome; option C is correct. Patients with primary hyperaldosteronism typically have hypertension, elevated plasma aldosterone levels, and suppressed plasma renin activity, unlike this patient; therefore, option A is incorrect. Patients with Bartter syndrome (especially type 3 or classic Bartter syndrome) may develop clinical manifestations in early adulthood and share phenotypic features with Gitelman syndrome and those with "pseudo-Bartter syndrome". The increased urinary calcium/creatinine ratio favors a diagnosis of Bartter syndrome over Gitelman syndrome because the urine calcium/creatinine ratio is usually low in the Gitelman syndrome (<44 mg/g). Hence, option B is incorrect. Urinary calcium excretion is generally in the high normal to high range in Bartter syndrome as noted in this patient. Pseudo-Bartter syndrome may be due to diuretic use, laxative abuse, a chronic chloride deficient diet, cyclical or surreptitious vomiting, excess losses of sodium chloride in sweat in cystic fibrosis, and congenital chloride diarrhea. Bartter syndrome is a salt losing tubulopathy due to genetic defects in transporters in the loop of Henle that ultimately interfere with the activity of the sodium-potassium-2 chloride cotransporter in the thick ascending limb of the loop of Henle. Hypovolemia results in secondary hyperaldosteronism as reflected by increases in both the plasma renin activity and the plasma aldosterone level. Individuals with Bartter syndrome have elevated

urine chloride levels, whereas those with pseudo-Bartter syndrome from vomiting have low urinary chloride levels (<15 mEq/L). Therefore, option D is incorrect. To note, an elevated urine chloride in the setting of hypokalemic metabolic alkalosis with low or normal blood pressure can also be seen in Gitelman syndrome, active diuretic abuse, and hypomagnesemia. Liddle syndrome is characterized by hypertension and suppressed plasma renin and aldosterone levels; therefore, option E is incorrect.

- Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF Jr.: The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 101**:** 1889-1916, 2016
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- Seyberth, HW: Pathophysiology and clinical presentations of salt-losing tubulopathies. *Pediatr Nephrol* 31**:** 407-418, 2016
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**Question 17**

**Educational objective: Manage calcineurin inhibitor-induced hyperkalemia**

**Answer B: Start chlorthalidone**

Hyperkalemia in the post-transplant setting is often multifactorial in etiology and may be due to reduced GFR, obstruction, or medication-related effects. The absence of hydronephrosis excludes obstruction as a potential cause, and the GFR is not sufficiently reduced in this case to account for the hyperkalemia. Medications that may contribute to hyperkalemia that are commonly used following transplantation include calcineurin inhibitors, the trimethoprim component of sulfamethoxazole-trimethoprim, renin-angiotensin-aldosterone antagonists, and nonselective beta-blockers. Tacrolimus is likely playing a significant role in the pathogenesis of this man's hypertension and hyperkalemia. One mechanism whereby calcineurin inhibitors induce hypertension is by increasing the abundance of phosphorylated NCC and the NCC-regulatory kinases WNK3, WNK4, and SPAK, resulting in a phenotype analogous to pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension). The resultant increased activity of NCC causes volume expansion and salt sensitive hypertension. In addition, alterations in WNK3, WNK4, and SPAK decrease the expression of renal outer medullary potassium channels in principal cells in the aldosterone sensitive portion of the distal tubule and collecting duct causing decreased renal potassium excretion and hyperkalemia. Thiazide diuretics have been shown to reverse these effects. Therefore, addition of chlorthalidone is the best management strategy to address this man's hyperkalemia and hypertension (option B is correct). The tacrolimus

level is appropriate for this patient who recently underwent kidney transplantation. Furthermore, a slight dose reduction is unlikely to significantly impact the hypertension and hyperkalemia. Hence, option A is incorrect. Fludrocortisone (option C) has been shown to improve posttransplant hyperkalemia; however, it may worsen sodium retention and would not be the best approach for this patient with concurrent hypertension. Sodium bicarbonate therapy would help correct metabolic acidosis and potentially augment potassium excretion in the collecting duct by enhancing lumen electronegativity. However, it could potentially worsen this man's hypervolemia and salt sensitive hypertension. Therefore, its use in this patient should be combined with diuretic therapy. Therefore, option D, sodium bicarbonate alone, is less attractive than option B.

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**Question 18**

**Educational objective: Identify complications of patiromer therapy**

**Answer A: Hypomagnesemia**

The US Food and Drug Administration recently approved patiromer calcium for the treatment of chronic hyperkalemia. It is a synthetic polymer with active alpha-fluoro carboxylic acid moieties paired with calcium as the exchange counter ion. It binds potassium in exchange for calcium in the distal colon where the concentration of potassium is the highest. Patiromer also binds magnesium and can cause hypomagnesemia, particularly in patients treated with proton pump inhibitors like this woman. The frequency of hypomagnesemia was 7.2% in the AMETHYST-DN trial (A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of Patiromer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy Receiving Angiotensin-converting Enzyme Inhibitor [ACEI] and/or Angiotensin II Receptor Blocker [ARB] Drugs, With or Without Spironolactone). Therefore, option A is correct. Hypercalcemia is a theoretical concern with patiromer because calcium is the exchange counter ion. No significant changes on calcium or phosphorus levels were noted over 52 weeks in the AMETHYST-DN trial; therefore, options B and D are incorrect. Metabolic alkalosis is a potential adverse effect of sodium zirconium cyclosilicate (ZS-9)

because it binds ammonium in the gut. This does not occur with patiromer calcium (option C is incorrect).

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## Question 19
**Educational objective: Diagnose a syndrome of apparent mineralocorticoid excess**
**Answer A: Decreased activity of 11β-hydroxysteroid dehydrogenase**

This woman has a syndrome of apparent mineralocorticoid excess based on the presence of hypertension, hypokalemic metabolic alkalosis with renal potassium wasting, and suppressed plasma renin activity and plasma aldosterone. The increased ratio of urine cortisol/cortisone with normal urinary cortisone excretion is most consistent with decreased activity of 11β-hydroxysteroid dehydrogenase (option A is correct). Some forms of imported tea derived from licorice extract contain glycyrrhetinic acid. Glycyrrhetinic acid competitively inhibits and decreases the expression of 11β-hydroxysteroid dehydrogenase. Impaired conversion of cortisol to the inactive metabolite cortisone results in activation of the mineralocorticoid receptor in the kidney by cortisol, which has a higher binding affinity for the receptor compared to aldosterone. Liddle syndrome is due to a gain-of-function mutation resulting in constitutive activation of the epithelial sodium channel in the aldosterone-sensitive portion of the distal tubule and collecting duct. Liddle syndrome also is characterized by the onset of hypertension early in life. Although both renin and aldosterone levels are suppressed, urinary free cortisol levels are normal; hence, option B is incorrect. This woman does not have the typical clinical features of Cushing syndrome. Furthermore, both urinary free cortisol and cortisone are increased in both Cushing syndrome and ectopic adrenocorticotropic hormone syndrome. Therefore, options C and D are incorrect.

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**Question 20**

**Educational objective: Know the potential adverse effects of sodium polystyrene sulfonate**

**Answer A: The frequency of colonic necrosis is approximately 0.1%**

In a retrospective single center study evaluating 123,391 adult inpatients, Watson and coworkers found that the frequency of colonic necrosis was 0.14%. The number needed to harm was 1395. Therefore, option A is correct. Sodium polystyrene sulfonate can potentially decrease the absorption of lithium and thyroxine; hence, option B is incorrect. Chernin and colleagues conducted an observational study evaluating the use of daily low dose sorbitol-free sodium polystyrene sulfonate in 14 patients with chronic kidney disease. They demonstrated efficacy over a median follow-up period of 14.5 months. No reports of colonic necrosis were noted. This is the only study providing long-term efficacy data of using sodium polystyrene sulfonate in CKD patients (option C is incorrect). Harel and coworkers conducted a systematic review of the literature and identified 58 cases with SPS associated gastrointestinal adverse effects (41 with sorbitol and 17 without sorbitol). The colon was the most common site of intestinal injury (76%), and those who had gastrointestinal injury incurred a mortality of 33%. About one-third of the individuals who sustained gastrointestinal injury received a sorbitol-free formulation of sodium polystyrene sulfonate. Therefore, option D is incorrect.

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**Question 21**

**Educational objective: Know the physiologic mechanism that accounts for salt-sensitive in individuals consuming a low potassium diet**

**Answer B: Increased activity of the NCC in the distal convoluted tubule**

Low potassium diets lead to low intracellular chloride in the distal tubule, activating with-no-lysine kinase 1 (option D is incorrect). Increased activity of with-no-lysine kinase 1 leads to enhanced phosphorylation of the sodium chloride cotransporter (NCC) in the distal tubule, thereby increasing the activity and expression of this transporter on the apical membrane. Increased NCC activity causes enhanced sodium retention and salt sensitive hypertension. Therefore, option B is correct. Low potassium diets decrease the secretion of aldosterone (option A is incorrect). High potassium diets increase the activity of the epithelial sodium channel (ENaC) in the aldosterone sensitive portion of the distal tubule cortical collecting duct, and low potassium diets likely produce an opposite effect. Hence, option C is incorrect. Conversely, high potassium diets cause a natriuretic response by inhibiting with-no-lysine 1 activity. As a result, there is decreased phosphorylation and decreased expression of NCC and increased delivery of sodium to the distal nephron. In addition, high potassium diets stimulate aldosterone secretion resulting in the activation of the epithelial sodium channel. Increased ENaC activity enhances the generation of a lumen negative potential and promotes kaliuresis. However, ENaC reabsorbs only a portion of the increased sodium delivered to the CCD as a result of decreased NCC activity yielding a net natriuresis.

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**Question 22**

**Educational objective: Evaluate hypokalemic metabolic alkalosis.**

**Answer C: Urine calcium-to-creatinine ratio**

Hypokalemic metabolic alkalosis and hypomagnesemia in this man with a life-long history of salt craving, absence of hypertension, increased renin and aldosterone, and absence of enteric losses or diuretic therapy is most compatible with Gitelman syndrome or Bartter syndrome. Evaluation of the urine calcium/creatinine ratio would be a relatively inexpensive simple test to help distinguish between

these diagnoses, and is the next best step in this man's diagnostic evaluation (option C is correct). A urine calcium/creatinine ratio <44 mg/g has a sensitivity of 80% for Gitelman syndrome. Gitelman syndrome is due to mutations in the sodium chloride cotransporter (NCC) gene SLC12A3 on chromosome 16. Genetic testing reveals a pathogenic mutation in 80% of individuals tested. Individuals with type 3 Bartter syndrome can also have hypokalemic metabolic alkalosis and hypomagnesemia, but are hypercalciuric with urine calcium/creatinine ratios that are typically >200 mg/g. A 24-h urine collection for potassium is not necessary because the relatively high urine potassium level in the setting of low serum potassium that confirms renal potassium wasting. It would be premature to request genetic testing for mutations in the *CLCNKB* gene until this man's urinary calcium excretion is assessed. Genetic testing, if desired, should ideally be guided by the phenotype, unless a more cost effective genetic testing panel is available. A patient with classic Gitelman syndrome and hypocalciuria should initially undergo testing for mutations in *SLC12A3*, the gene that encodes the sodium chloride cotransporter NCC. Genetic testing for mutations in the mutations in the *CLCNKB* gene could be considered in individuals with a phenotype that evolves from one that is like Bartter syndrome to one that resembles Gitelman syndrome. Although the response to thiazide diuretics has improved sensitivity for the diagnosis of Gitelman syndrome, it carries a risk of significant hypovolemia and hypokalemia, and is not recommended as a first-line diagnostic test.

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**Question 23**
**Educational objective: Understand the mechanism of cisplatin-induced hypomagnesemia.**
**Answer D: The early distal convoluted tubule**

In a rat model of cisplatin nephrotoxicity, Ledeganck and coworkers found that epidermal growth factor is downregulated. Because epidermal growth factor stimulates trafficking and expression of the magnesium transporter transient receptor potential melastatin-6 (TRPM6) on the apical membrane, its downregulation causes decreased expression of TRPM6 in the early distal convoluted tubule and renal magnesium wasting resulting in hypomagnesemia. Cisplatin-induced injury of the early distal tubule also disrupts the activity of the sodium chloride cotransporter NCC causing natriuresis and hypovolemia. Because calcium transport via the transporter transient receptor potential melastatin-5 (TRMP5) is augmented when there is decreased NCC activity, calcium entry into the early distal tubule epithelial cells is enhanced. In addition, there is increased proximal tubular reabsorption of calcium as a result of hypovolemia. These two factors combine to cause the hypocalciuria characteristic of cisplatin nephrotoxicity. Hypomagnesemia causes renal potassium wasting because it stimulates the expression of the renal outer medullary potassium channel (ROMK) in the cortical collecting ducts. Dysfunction of the thick ascending limb of the loop of Henle would cause hypercalciuria, not hypocalciuria as noted in this case, because impaired transport of potassium out of the tubular epithelium enhances the lumen negative potential thereby decreasing the electrochemical gradient that drives calcium reabsorption in this segment of the nephron. Therefore, option A is incorrect. Injury to the medullary collecting duct and the epithelial sodium channel would cause enhanced reabsorption of magnesium in the collecting duct and hypomagnesuria (option B is incorrect). The thin descending limb of the loop of Henle does not play a significant role in magnesium reabsorption; therefore, injury to this nephron segment is unlikely to cause hypermagnesuria and hypomagnesemia (option C is incorrect).

- Subramanya AR, Ellison DH: Distal convoluted tubule. *Clin J Am Soc Nephrol* 9: 2147-216, 2014
- Huang CL, Kuo E: Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol* 18: 2649–2652, 2007
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**Question 24**
**Educational objective: Diagnose proximal renal tubular acidosis**
**Answer E: Proximal renal tubular acidosis**
The findings of hypokalemia, a low serum uric acid level, nonanion gap metabolic acidosis, renal phosphate wasting, a urine pH <5.5, submaximal ammonium urine levels despite acidemia, and low molecular weight proteinuria are most consistent with proximal renal tubular acidosis; option E is correct. Renal phosphate wasting is evident based on the high fractional excretion of phosphate noted

in this woman. The fractional of phosphate ($FE_{Phos}$) is calculated by the following equation. $FE_{Phos} = (U/P_{Phos} \div U/P_{creatinine}) \times 100\%$. In this case, $FE_{Phos} = (25/1.1 \div 100/1.3) \times 100\% = 23/77 \times 100\% = 30\%$. A $FE_{Phos} >5\%$ is consistent with renal phosphate wasting. This woman most likely has proximal renal tubular acidosis consequent to deferasirox therapy. Deferasirox is an iron-chelating agent used to treat iron overload most commonly seen in transfusion dependent diseases such as myelodysplastic syndrome or beta-thalassemia major. The low urine pH and findings indicative of proximal tubular injury make distal renal tubular acidosis less likely (option A is incorrect). Tumor-induced osteomalacia would cause isolated hypophosphatemia without metabolic acidosis as noted in this case (option B is incorrect). Spurious hypophosphatemia may be caused by paraprotein interference with specific phosphate assays. This patient had no clear evidence of a paraprotein. In addition, spurious hypophosphatemia would not account the observed renal phosphate wasting and acidosis. Gastrointestinal losses of bicarbonate would generally be associated with a low fractional excretion of phosphate and a higher level of urine ammonium excretion (option D is incorrect).

- Haque SK, Ariceta G, Batlle D: Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. *Nephrol Dial Transplant* 27:4273-4287, 2012
- Hall AM, Bass P, Unwin RJ: Drug-induced renal Fanconi syndrome. *QJM* 107: 261-269, 2014

**Question 25**
**Educational objective: Diagnose incomplete distal renal tubular acidosis**
**Answer D: Incomplete distal renal tubular acidosis (type 1)**
The history of recurrent calcium phosphate stones and low urine citrate excretion are most consistent with a diagnosis of incomplete distal renal tubular acidosis; option D is correct. Documenting impairment in urinary acidification after an acid load with ammonium chloride can make the diagnosis more definitively. Individuals with type 4 RTA have hyperkalemic metabolic acidosis, do not develop recurrent kidney stones, and are able to acidify the urine to a pH <5.5 during metabolic acidosis (option A is incorrect). This man does not have evidence of proximal tubular dysfunction such as hyperphosphaturia, low molecular weight proteinuria, or glycosuria characteristic of proximal renal tubular acidosis (option B is incorrect). Dent disease is an X-linked recessive disorder that manifests with either calcium oxalate or calcium phosphate stones that manifest during childhood, hypercalciuria, hyperphosphaturia, low molecular weight proteinuria, polyuria, and progressive chronic kidney disease. Urinary acidification and citrate excretion are usually normal in Dent disease when the GFR preserved, although proximal tubular injury and Fanconi syndrome may occur. The age of onset of kidney stones and the biochemical abnormalities in this man are not consistent with Dent disease; hence, option C is incorrect.

- Batlle D, Haque SK: Genetic causes and mechanisms of distal renal tubular acidosis. *Nephrol Dial Transplant* 27: 3691–3704, 2012

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**Question 26**

**Educational objective: Recognize Pendred syndrome**

**Answer C: An 18-year-old woman with sensorineural hearing loss and goiter**

The 18-year-old woman with sensorineural hearing loss and goiter most likely has Pendred syndrome, an autosomal recessive condition due to decreased activity of pendrin. Pendrin is a chloride-bicarbonate exchanger localized on the apical membrane of beta-intercalated cells. Pendrin appears to have an important role not only in ameliorating metabolic alkalosis, but also in maintaining volume. Knockout of pendrin in animal models eliminates chloride reabsorption in the cortical collecting duct. In Pendred syndrome, increased activity of the sodium chloride cotransporter (NCC) in the distal tubule compensates for the loss of function of pendrin. Inhibition of NCC by thiazide diuretics causes significant sodium chloride wasting, hypokalemia, hypovolemia, and life threatening metabolic alkalosis in Pendred syndrome; therefore, option C is correct. Individuals with glucocorticoid-remediable aldosteronism (GRA) develop marked hypokalemia in response to thiazide diuretics because increased availability of luminal sodium in response to the thiazide facilitates electrogenic sodium reabsorption by principal cells that drives potassium secretion. Hypovolemia is not an issue because the extracellular fluid volume is expanded in individuals with GRA (option A is incorrect). Similarly, the extracellular fluid volume is expanded in Liddle syndrome, preventing marked hypovolemia in response to thiazide diuretics (option B is incorrect). Monotherapy with thiazides should not cause severe hypovolemia and alkalosis (Choice D is incorrect), although hypovolemia and metabolic alkalosis may be more pronounced when used in combination with loop diuretics.

- Pela I, Bigozzi M, Bianchi B: Profound hypokalemia and hypochloremic metabolic alkalosis during thiazide therapy in a child with Pendred syndrome. *Clin Nephrol* 69: 450-453, 2008
- Soleimani M, Barone S, Xu J, Shull GE, Siddiqui F, Zahedi K, Amlal H: Double knockout of pendrin and Na-Cl cotransporter (NCC) causes severe salt wasting, volume depletion, and renal failure. *Proc Natl Acad Sci U S A* 109: 13368-13373, 2012
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**Question 27**

**Educational objective: Diagnose the cause of metabolic alkalosis.**

**Answer B: Gentamicin**

The differential diagnosis of hypokalemic metabolic alkalosis and normal to low extracellular fluid volume status includes diuretics, gastric fluid loss though vomiting or nasogastric suction, Gitelman syndrome, Bartter syndrome, gentamicin-induced Bartter syndrome, and high-dose penicillin therapy. A syndrome that resembles Bartter syndrome may occur after exposure to greater than 1.2 grams of gentamicin. Aminoglycoside-induced Bartter-like syndrome is characterized by hypokalemic metabolic

alkalosis, hypomagnesemia, and hypocalcemia. The increased urine sodium, chloride, and potassium levels are consistent with active diuretic use, Bartter and Gitelman syndromes, and colonic stimulant laxative abuse (when gastrointestinal bicarbonate losses are less than urinary ammonium excretion). The most likely diagnosis is Bartter syndrome secondary to gentamicin because of the absence of diuretic or laxative exposure. Hence, option B is correct. Aminoglycosides are divalent cations that activate the calcium sensing receptor (CaSR) in the thick ascending limb of Henle. As a result, intracellular cyclic adenosine monophosphate (cAMP) production decreases, resulting in increased arachidonic acid (20-hydroxyeicosatetraenoic acid). Arachidonic acid inhibits ROMK and NKCC2 causing inhibition of sodium/potassium/chloride reabsorption and abolition of the normally lumen-positive potential in the thick ascending limb. As a result, a loop diuretic effect ensues that also inhibits calcium and magnesium uptake via the paracellular pathway. Consequently, there is urinary calcium and magnesium wasting with concomitant reductions of serum concentrations of these divalent cations. The Bartter-like syndrome, which is caused by CaSR activation, is distinct from isolated NKCC2 or ROMK dysfunction, which usually results in hypercalciuria with normal urinary magnesium excretion. The Bartter-like syndrome associated with aminoglycosides usually persists for 2 to 6 weeks after discontinuation of gentamicin and requires vigilant monitoring and supplementation of potassium, calcium, and magnesium. It is not yet clear whether the incidence of aminoglycoside-induced Bartter syndrome is increased in patients with cystic fibrosis. Nasogastric suctioning can cause metabolic alkalosis and hypokalemia, but it is also characterized by low urine chloride excretion (urine chloride < 15 mEq/L); therefore, option A is incorrect. Both urine sodium and chloride levels are low in posthypercapnic metabolic alkalosis (option C is incorrect). Individuals with cystic fibrosis can develop hypovolemia and metabolic alkalosis from excess sodium chloride losses in sweat, particularly during summer months. However, the urine sodium and chloride levels should be low (option D is incorrect). Increased delivery of non-reabsorbable anion metabolites of penicillin during high dose parenteral therapy can result in generation of a lumen negative potential, facilitating excretion of potassium and hydrogen ions, causing hypokalemic metabolic alkalosis. This effect is most prominent when there is concurrent hypovolemia leading to increased proximal chloride reabsorption and urine devoid of chloride. This is not known to occur with high dose ceftazidime therapy (option E is incorrect).

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- Chou CL, Chen YH, Chau T, Lin SH: Acquired Bartter-like syndrome associated with gentamicin administration. *Am J Med Sci* 329:144-149, 2005
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**Question 28**

**Educational objective: Evaluate incomplete distal renal tubular acidosis**

**Answer A: Ammonium chloride challenge test**

Incomplete distal renal tubular acidosis should always be considered in patients with idiopathic renal calculi with alkaline urine and low urinary citrate levels. Such findings may be seen in patients with Sjögren syndrome, children with posterior urethral valve disease, and patients with amphotericin toxicity. Kidney stones in these conditions are primarily due to low urinary citrate levels combined with a high urine pH, which favor the generation of calcium phosphate kidney stones. Calcium phosphate stones may be the first sign of an abnormality in acid secretion in patients with incomplete distal renal tubular acidosis. This diagnosis is best confirmed by the ammonium chloride challenge test. Ammonium chloride is administered at a dose of 0.1 g per kilogram of body weight followed by hourly urine collection and urine pH measurement for 2-8 hours after administration. Failure to acidify urine to a pH below 5.3 supports the diagnosis of incomplete distal renal tubular acidosis. Therefore, option A is correct. The furosemide-fludrocortisone challenge test has been proposed as an alternative and simplified method to diagnosis incomplete distal renal tubular acidosis. In normal individuals, furosemide-induced enhanced distal sodium delivery reduces urinary pH. The urine pH remains >5.5 in patients with distal renal tubular acidosis after treatment with 40–80 mg of furosemide and 1 mg of fludrocortisone. Measurement of the fractional excretion of bicarbonate after the serum bicarbonate is raised above normal values can be used to confirm the diagnosis of proximal renal tubular acidosis. It would have no diagnostic value in this woman with suspected incomplete distal renal tubular acidosis (option B is incorrect). The recent episode of uncomplicated nephrolithiasis is unlikely to significantly alter the composition of the urine parameters (option C is incorrect). The urine osmolal gap can be used to estimate urine ammonium excretion, but would be superfluous in this case because the ammonium excretion has been directly measured in this woman (option D is incorrect).

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**Question 29**

**Educational objective: Manage hyperkalemia**

**Answer C: Isotonic sodium bicarbonate infusion**

The most appropriate management for this man's hyperkalemia is volume expansion with isotonic sodium bicarbonate; option C is correct. Hypovolemia may contribute to the pathogenesis of hyperkalemia through several mechanisms.

1. It decreases the availability of sodium for electrogenic reabsorption via the epithelial sodium channel in the cortical collecting duct (CCD)
2. It decreases the volume of tubular fluid available for potassium secretion
3. It limits flow-mediated activation of the stretch activated maxi-potassium (maxi-K) or big potassium (BK) channels on the apical surface of principal and alpha-intercalated cells.

A sodium bicarbonate infusion would not only correct the hypovolemia, but would enhance lumen electronegativity in the cortical collecting, thereby facilitating potassium secretion. Fludrocortisone, an exogenous mineralocorticoid, facilitates potassium secretion in the CCD by enhancing sodium uptake and thus creating a favorable electrochemical gradient for potassium secretion. This response would be blunted in this patent with hypovolemia and decreased flow and sodium delivery to the potassium secretory site in the CCD. Hence, option A is less attractive. Fludrocortisone could be used as adjunctive therapy once the hypovolemia is corrected, but its long-term use is often limited by salt sensitive hypertension often seen in kidney transplant recipients maintained on calcineurin inhibitors. Patiromer is a nonabsorbable synthetic polymer cation exchange resin that exchanges potassium for calcium in the gut. Patiromer should not be used alone in the emergency treatment of life-threatening hyperkalemia because of its delayed onset of action. Bushinsky reported that patiromer decreased the serum potassium by 0.23 mEq/L after 7 hours. Hemodialysis (option D) would only be warranted if the

hyperkalemia persisted despite correction of hypovolemia and intravenous insulin, particularly if the urine volume remained low.

- Bushinsky DA: Patiromer induces a rapid and sustain potassium lowering in CKD patients with hyperkalemia. *Kidney Int* 88: 1427–1433, 2015
- Sterns RH, Grieff M, Bernstein PL: Treatment of hyperkalemia: something old, something new. *Kidney Int* 89**:** 546-554, 2016


**Question 30**

**Educational objective: Manage diuretic therapy.**

**Answer D: Continue current regimen**

This woman has persistent evidence of venous and pulmonary congestion. Even though the BUN and serum creatinine are rising, the degree of renal impairment is acceptable, and continuation of the current diuretic regimen is the most appropriate management strategy (option D is correct). The daily urine volume and estimated sodium output confirm an adequate diuretic response. Testani and coworkers found that an estimated cumulative sodium output of <50 mEq with each dose of bumetanide reliably predicted a poor diuretic response with twice daily dosing. This woman's sodium output is clearly above this threshold at 140 mEq (280 mEq/d on twice daily dosing). Cumulative sodium output can be estimated by the equation,

Sodium output (mEq) = eGFR × (BSA/1.73 m$^2$) × SCr /UCr × 60 min × 2.5 hr × (UNa/1000 ml).

This woman has demonstrated an adequate response to intravenous bumetanide that does not warrant initiation of ultrafiltration or other forms of renal replacement therapy (option A is incorrect). It would not be necessary to hold or decrease the dose of bumetanide until a stable serum creatinine is documented given the modest change in kidney function and persistent venous and pulmonary congestion, although close follow up of the renal function is indicated; therefore, options B and C are less attractive.

- Verbrugge FH, Mullens W, Tang WHW: Management of Cardio-Renal Syndrome and Diuretic Resistance. *Curr Treat Options Cardio Med* 18: 11, 2016
- Testani JM, Hanberg JS, Cheng S, Rao V, Onyebeke C, Laur O, Kula A, Chen M, Wilson FP, Darlington A, Bellumkonda L, Jacoby D, Tang WH, Parikh CR: Rapid and Highly Accurate Prediction of Poor Loop Diuretic Natriuretic Response in Patients With Heart Failure. *Circ Heart Fail* 9: e002370, 2016