Diuretics in States of Volume Overload: Core Curriculum 2022

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Volume overload, defined as excess total body sodium and water with expansion of extracellular fluid volume, characterizes common disorders such as congestive heart failure, end-stage liver disease, chronic kidney disease, and nephrotic syndrome. Diuretics are the cornerstone of therapy for volume overload and comprise several classes whose mechanisms of action, pharmacokinetics, indications, and adverse effects are essential principles of nephrology. Loop diuretics are typically the first-line treatment in the management of hypervolemia, with additional drug classes indicated in cases of diuretic resistance and electrolyte or acid-base disorders. Separately, clinical trials highlight improved outcomes in some states of volume overload, such as loop diuretics and sodium/glucose cotransporter 2 inhibitors in patients with congestive heart failure. Resistance to diuretics is a frequent, multifactorial clinical challenge that requires creative and physiology-based solutions. In this installment of *AJKD*'s Core Curriculum in Nephrology, we discuss the pharmacology and therapeutic use of diuretics in states of volume overload and strategies to overcome diuretic resistance.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Case 1: *A 56-year-old man is admitted to the hospital with worsening dyspnea and 8-kg weight gain and is diagnosed with acute decompensated heart failure (ADHF). He has a history of hypertension, type 2 diabetes, coronary artery disease, chronic kidney disease (CKD) glomerular filtration rate (GFR) category 3b and albuminuria category 2 (G3bA2), and ischemic cardiomyopathy with ejection fraction 30%. He is adherent to prescribed medications, including losartan, furosemide (40 mg twice daily), atorvastatin, and insulin. Blood pressure (BP) is 162/92 mm Hg and heart rate 104 beats per minute. Physical examination reveals an S3 gallop, bilateral crackles, and pitting edema (3+). Admission laboratory data include serum sodium level of 132 mEq/L, serum potassium level of 5.2 mEq/L, serum urea nitrogen level of 63 mg/dL, and serum creatinine (Scr) level of 2.1 mg/dL (baseline, 1.4 mg/dL).*

Question 1: Which of the following is the next best step in management?

a) Prescribe furosemide intravenous (IV) infusion
b) Prescribe metolazone
c) Prescribe dapagliflozin
d) Prescribe isolated ultrafiltration
e) Discontinue losartan

For the answer to the question, see the following text.

Volume overload is defined as excess total body sodium and water with expansion of extracellular fluid volume. Volume overload characterizes several common disorders, including congestive heart failure (CHF), cirrhosis or end-stage liver disease (ESLD), CKD (including kidney failure), and nephrotic syndrome. The specific pathophysiology of these diseases varies, but most patients present with one or more signs or symptoms of hypertension, peripheral edema, pulmonary congestion, and ascites. The Agency for Healthcare Research and Quality estimated that volume-overload states such as CHF accounted for 1.1 million hospitalizations at a cost of $13.6 billion in the United States in 2017, whereas kidney and liver disease hospitalizations cost a combined $9.7 billion.

Diuretics are the cornerstone of therapy for volume overload. There are several classes of diuretics, whose mechanisms of action, pharmacokinetics, and clinical use constitute basic principles of nephrology. Diuretic resistance is a frequent clinical challenge caused by many factors (Box 1). The patient in case 1 presents with ADHF associated with resistance to oral furosemide. The best next step in management is changing furosemide from oral to IV dosing, thereby bypassing slowed absorption from gastrointestinal (GI) edema. Additionally, most contemporary guidelines suggest using 2-2.5 times the home dose (here, 80-100 mg IV). Alternatively, furosemide could be changed to an equivalent dose of bumetanide or torsemide; some small studies have shown better intermediate outcomes with torsemide for symptomatic decongestion, but large outcomes

Box 1. Causes of Diuretic Resistance, With Examples

- No volume overload (wrong diagnosis)
  - Venous stasis
  - Lymphedema, lipedema
- Nonadherence
  - Excess salt intake
  - Nonadherence to medication
- Decreased drug delivery
  - Decreased absorption (gut edema)
  - Inadequate dose/frequency
  - Hypoalbuminemia
- Decreased drug secretion
  - Decreased kidney blood flow: AKI/CKD, decreased EABV
  - Tubule transport inhibition: FFAs, bile acids, organic acids, NSAIDs, indoxyl sulfate, *p*-cresyl sulfate
  - Decreased kidney mass
- Decreased kidney response
  - Distal tubule hypertrophy
  - Renin-angiotensin-aldosterone activation

Based on information in Hoorn and Ellison, 2017(*Am J Kidney Dis.* https://doi.org/10.1053/j.ajkd.2016.08.027). Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; EABV, effective arterial blood volume; FFA, free fatty acid; NSAID, nonsteroidal anti-inflammatory drug.

studies conflict as to whether loop diuretic choice affects long-term outcomes, including mortality. Metolazone could be added to block distal tubule sodium reabsorption in conjunction with, but not in place of, IV furosemide. Dapagliflozin improves outcomes in CHF but would not replace an IV loop diuretic for prompt decongestion. Isolated ultrafiltration removes fluid as effectively as furosemide but is associated with more frequent adverse events. Stopping losartan may be necessary if acute kidney injury (AKI) or hyperkalemia worsen, but these conditions frequently improve with diuresis alone. So, the correct answer to question 1 is (a).

In this installment of *AJKD*'s Core Curriculum in Nephrology, we discuss the pharmacology and therapeutic use of diuretics in states of volume overload. We also review strategies to overcome diuretic resistance.

Pharmacokinetics

Case 1, continued: *Furosemide 40 mg IV followed by an infusion of 5 mg/h is administered, and urine output increases to 2.4 L/d. After 2 days, the patient's dyspnea and peripheral edema have improved, and BP has decreased to 146/84 mm Hg. Scr has also decreased from 2.1 to 1.7 mg/dL. Preparing the patient for discharge, the inpatient team converts medications from IV to oral dosing and schedules primary care follow-up within 1 week.*

Question 2: Which of the following is the most appropriate diuretic regimen for discharge?

a) Furosemide 120 mg twice daily and metolazone 10 mg/d
b) Furosemide 80 mg twice daily
c) Furosemide 160 mg/d
d) Bumetanide 4 mg twice daily
e) Bumetanide 4 mg/d

For the answer to the question, see the following text.

Pharmacokinetics describe how a drug is absorbed, distributed, metabolized, and eliminated by the body. For example, furosemide is absorbed similarly in the stomach and duodenum, although gastric absorption is slow and includes first-pass metabolism. This effect may account for the lower (50%-60%) bioavailability of furosemide compared with other loop diuretics such as bumetanide and torsemide (>80%). Such differences in bioavailability have implications for IV-to-oral dosing conversions: generally, the furosemide dose should be doubled when making this change, whereas bumetanide and torsemide doses should stay the same, although these rules are only approximations. Ultimately, the effective dose is determined by the urine output response. GI tract edema decreases the velocity but not the total amount of furosemide absorbed. However, this slowed absorption may prevent orally administered furosemide from reaching its threshold plasma concentration (Fig 1A). Finally, the dose-response curve for loop diuretic agents is sigmoidal and logarithmic, so exponential dose increases may be needed for patients who do not show a response to an algorithmic or empirical dose (Fig 1B). Conversely, doses that yield plasma concentrations greater than the ceiling may increase toxicity without increasing response.

Once absorbed, most diuretics bind to serum albumin for distribution, followed by metabolism and elimination by the liver and kidneys. Hypoalbuminemia and impaired renal blood flow (as in AKI and CKD) decrease diuretic delivery, so albumin and loop diuretic coinfusion has been proposed to improve drug response, but this

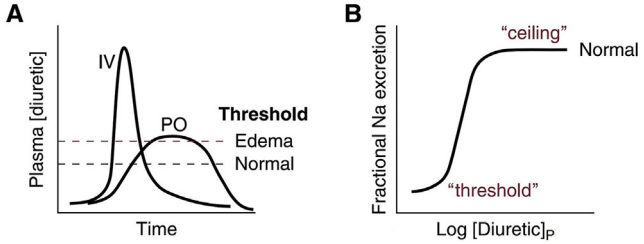

Figure 1. (A) Plasma diuretic concentration versus time. Dashed lines show natriuretic thresholds for individuals with and without edema. (B) Dose-response curve for loop diuretic plasma concentration. Abbreviations: IV, intravenous; PO, oral. Reproduced from Ellison, 2019 (*Clin J Am Soc Nephrol.* https://doi.org/10.2215/cjn.09630818) with permission of the copyright holder.

practice has not been beneficial in critically ill adult patients. Furosemide is metabolized completely by the kidneys (35% furosemide glucuronide and 65% parent molecule excretion), whereas torsemide is metabolized mainly by the liver. Triamterene is a prodrug that requires hepatic activation to hydroxytriamterene, so it is relatively ineffective in ESLD. Routes of diuretic metabolism and elimination may be important considerations for patients with kidney or liver disease (Table 1).

Peak serum concentrations of loop diuretics occur within 0.5-2 hours, even though drug effects may last for 6-8 hours, especially with impaired kidney, heart, or liver function. The short elimination half-life ($t_{1/2}$) of most loop diuretics, except possibly torsemide, means they are typically dosed at least twice daily. Despite this short $t_{1/2}$, more frequent administration than twice daily is usually unnecessary because sodium intake is zero during sleep. Conversely, if loop diuretics are prescribed only once daily, the kidneys are diuretic-free for many hours, allowing considerable rebound sodium reabsorption in most cases. On the contrary, thiazide and distal diuretics have much longer $t_{1/2}$ values and may be given daily. A new extended-release preparation of torsemide has been approved by the US Food and Drug Administration (FDA) for the treatment of edema from heart and kidney failure.

In case 1, the patient was initially prescribed a furosemide loading dose of 80 mg IV to rapidly achieve a therapeutic serum level, followed by a maintenance dose of 5 mg/h (120 mg/d) IV to maintain a steady state; this management strategy has effectively achieved decongestion. This dose is equivalent to 240 mg/d orally, which should be given as 120 mg twice daily to avoid postdiuretic sodium reabsorption. However, because this patient's signs and symptoms of ADHF and AKI resolved and 2.4 L/d urine output is no longer necessary, a lower oral dose of furosemide, such as 80 mg twice daily, may be appropriate. Furosemide 120 mg twice daily with metolazone 10 mg/d would further increase diuresis and could cause hypovolemia and/or hypokalemia. Similarly, bumetanide 4 mg orally twice daily, which is equivalent to furosemide 160 mg IV twice daily or 320 mg orally twice daily, would also risk hypovolemia. Unless sodium intake can be severely restricted, neither furosemide nor bumetanide should be dosed once daily. The correct answer to question 2 is (b).

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Table 1. Pharmacokinetics of Diuretics

Diuretic	Bioavailability	Equivalent Dose, mg	Metabolism (Kidney/Liver)	Elimination $t_{1/2}$, h			
				Normal	CKD	CHF	ESLD
Loop							
Furosemide	50%-60% (10%-100%)[a]	40	100%/0%	1.5-2	2.6-2.8	2.7	2.5
Bumetanide	80%-100%	1	50%/50%	1	1.6	1.3	2.3
Torsemide	68%-100%	20	20%/80%	3-4	4-5	6	8
Thiazide							
HCTZ	65%-75%	25	100%/0%	6-15	↑	↔	↔
Chlorthalidone	60%-72%	12.5	100%/0%	40-60	↑	↔	↔
Metolazone	65%-90%	2.5	70%-95%/5%-30%	14-20	↑	↔	↔
Distal							
Amiloride	50%	10	50%/–[b]	6-26	100	?	↔
Triamterene	52%-80%	100	20%/80%	2-5	↑	?	–[c]
Spironolactone	>90%	25	0%/100%	>15[d]	↔	?	↔

Based on information in Hoorn and Ellison, 2017 (*Am J Kidney Dis.* https://doi.org/10.1053/j.ajkd.2016.08.027). Abbreviations: $t_{1/2}$, half-life; AKI, acute kidney injury; CHF, congestive heart failure; CKD, chronic kidney disease; EABV, effective arterial blood volume; ESLD, end-stage liver disease; FFA, free fatty acid; HCTZ, hydrochlorothiazide.

[a]The usual range is taken as 50%-60%, but some have reported a range as great as 10%-100%.

[b]Amiloride is 50% excreted in the stool.

[c]Triamterene requires hepatic activation and is considered inactive in ESLD.

[d]Spironolactone undergoes rapid hepatic breakdown to active metabolites; parent molecule elimination $t_{1/2}$ = 1.5 h.

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Classes of Diuretics

Case 2: *A 63-year-old woman presents to the clinic for ongoing management of CHF from ischemic cardiomyopathy (ejection fraction 22%) and CKD G3bA2 from type 2 diabetes. She has been hospitalized repeatedly with hyperkalemia, AKI, and ADHF, and lisinopril was finally discontinued after several attempts to maintain a dose of 2.5-5 mg/d. She is currently taking furosemide 40 mg twice daily and now reports slightly increased edema but no difficulty breathing. BP is 146/86 mm Hg, heart rate 68 beats per minute, and respiratory rate 14 per minute. Physical examination reveals an S3 gallop, clear lung fields, and pitting edema (2+). Serum potassium level is 5.6 mEq/L, total CO_2 level is 40 mEq/L, and Scr is 1.5 mg/dL (at baseline). Arterial blood gas reveals pH 7.49, partial pressure of CO_2 of 55 mm Hg, partial pressure of O_2 of 90 mm Hg, and bicarbonate level of 41 mEq/L.*

Question 3: Which of the following is the next best step in management?

a) Increase furosemide to 80 mg twice daily
b) Prescribe chlorthalidone 12.5 mg/d

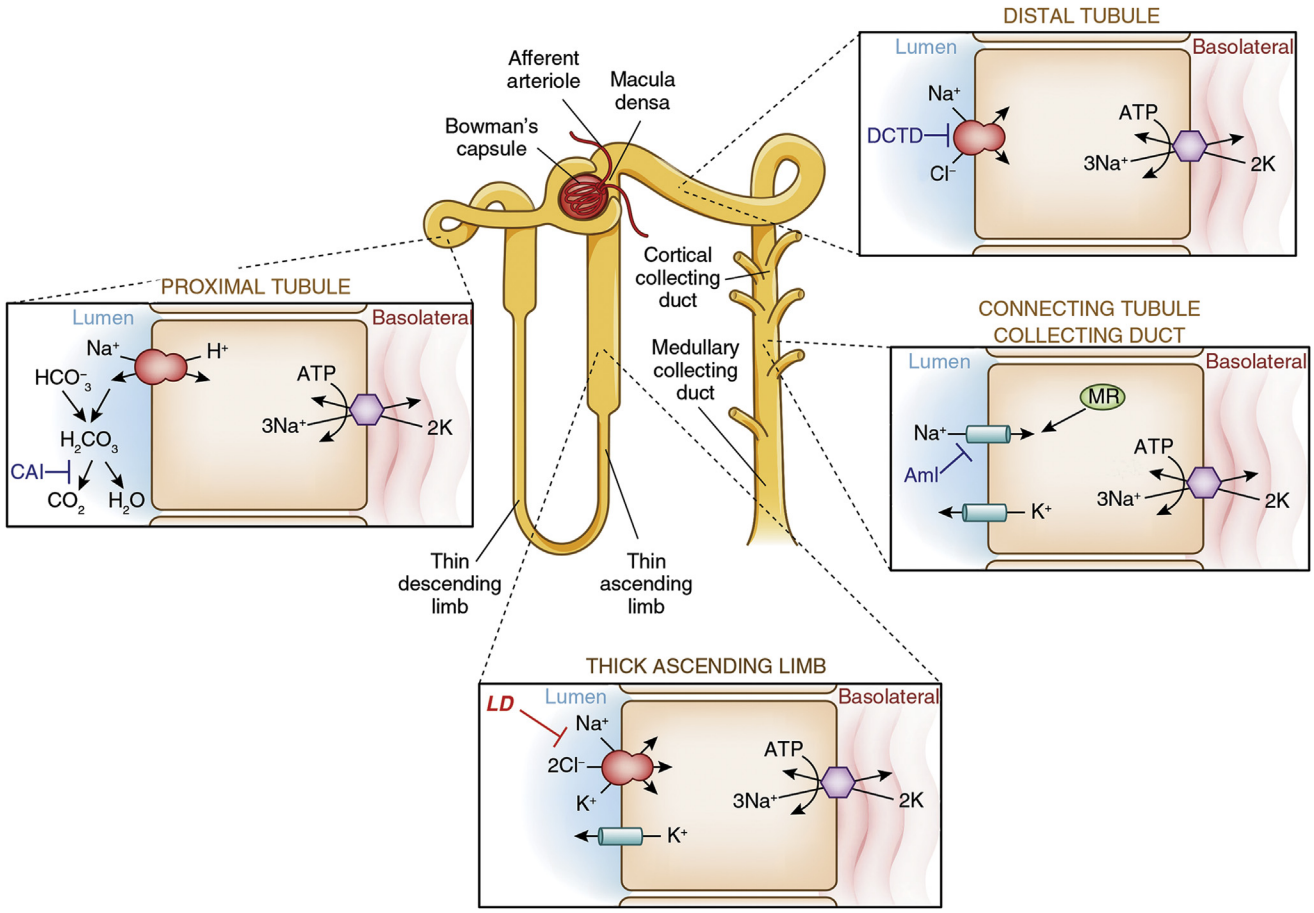

Figure 2. Sites of sodium reabsorption and diuretic action. Abbreviations: Aml, amiloride (and triamterene); CAI, carbonic anhydrase inhibitors; DCTD, distal convoluted tubule diuretics (eg, thiazides); LD, loop diuretics; MR, mineralocorticoid receptor. Reproduced from Ellison, 2019 (*Clin J Am Soc Nephrol*. https://doi.org/10.2215/cjn.09630818) with permission of the copyright holder.

c) Prescribe spironolactone 25 mg/d
d) Prescribe acetazolamide 250 mg/d
e) Prescribe sodium zirconium cyclosilicate 10 g/d

For the answer to the question, see the following text.

Sulfonamides

Sulfonamides are characterized by a $-SO_2NH_2$ group and include loop diuretics, benzothiadiazide or thiazide-like diuretics (thiazides), and carbonic anhydrase (CA) inhibitors (CAIs). Because these drugs are 91%-99% albumin-bound anions, they are first taken up by proximal tubule cells by organic anion transporters (OATs) and are then secreted into the urine via multidrug resistance-associated protein 4 (MRP4). Although sulfonamide diuretics are categorized by their primary site of action (Fig 2), several drugs act at more than one site, causing overlap between the classes. For instance, the thiazide diuretics hydrochlorothiazide (HCTZ) and metolazone block not only the distal sodium/chloride cotransporter (NCC) but also the proximal tubule sodium/hydrogen exchanger or CA, respectively, and thus act as weak CAIs as well.

Sulfonamide diuretics are often avoided in sulfa-allergic patients, but this practice may be unwarranted because most patients who report a sulfa allergy can tolerate them. Allergic reactions to these drugs seem to result from generalized hypersensitivity rather than specific cross-reactivity to the sulfonamide group. Sulfonamide antibiotics contain an aromatic amine and undergo hepatic oxidation to hydroxylamines, which may mediate allergic reactions in susceptible patients, whereas sulfonamide diuretics do not contain this aromatic amine and are metabolized differently.

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Loop Diuretics

Loop diuretics antagonize the sodium/potassium/chloride cotransporter (NKCC2) in the thick ascending limb of the loop of Henle. This drug class includes the sulfonamides furosemide, bumetanide, and torsemide and the nonsulfonamide ethacrynic acid. Loop diuretics also block sodium chloride reabsorption through an NKCC2 splice variant in the macula densa, disrupting tubuloglomerular feedback and maintaining GFR despite ongoing diuresis. Blockade of sodium chloride entry into macula densa cells also causes volume-independent renin release from the juxtaglomerular apparatus and subsequent renin-angiotensin-aldosterone system (RAS) activation. Because the thick ascending limb reabsorbs 20%-25% of the filtered sodium load, these drugs are among the strongest diuretics available.

Loop diuretics cause several adverse effects. Hypotension is caused by diuresis as well as, and more immediately, by vasodilation from vascular sodium/potassium/chloride cotransporter (NKCC1) inhibition. Hypokalemia and metabolic alkalosis result from increased sodium delivery to the distal nephron and activation of the RAS (Table 2). By blocking potassium recycling (into the cell via NKCC2 and back to the lumen via the renal outer medullary K [ROMK] channel), loop diuretics reduce the lumen-positive voltage gradient in the thick ascending limb, thereby inhibiting paracellular calcium and magnesium reabsorption (Fig 3). Loop diuretics may cause hyperuricemia, probably by competitively inhibiting urate excretion via OAT, MRP4, or sodium phosphate transporter 4 in the proximal tubule. Importantly, NKCC2 antagonism deprives the renal medulla of half of the osmolytes it needs to maintain hypertonicity, preventing water reabsorption and occasionally causing hypernatremia. Ototoxicity is an uncommon complication of loop diuretics and includes reversible ischemia and disruption of cochlear action potentials, as well as irreversible hair cell loss, notably when high doses (eg, furosemide ≥25 mg/min IV) are given with aminoglycosides.

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Table 2. Effects of Diuretics on Serum Concentration of Electrolytes, Acid-Base Balance, and Other Parameters

Class	Serum Concentration						Miscellaneous
	K^+	Ca^{2+}	Mg^{2+}	$Urate^-$	Na^+	H^+	
Loop	↓	↓	↓	↑	↑	↓	Ototoxicity with AG
Thiazide	↓	↑	↓	↑	↓	↓	Insulin resistance
CAI	↓	↓	↓	↔	↓	↑	CaP stones
K-sparing	↑	↑[a]	↑	↑	↑↓[b]	↑	Androgen blockade
SGLT2i	↔/↑	↔	↑	↓	↑	↔	Euglycemic DKA
Vaptan	↔/↓	↔	↔	↔	↑	↔	–
Osmotic	↑↓[c]	↓	↓	↓	↑↓[c]	↑	–

Based on information in Greenberg, 2000 (*Am J Med Sci.* 319[1]:10-24). Abbreviations: AG, aminoglycoside; CAI, carbonic anhydrase inhibitor; DKA, diabetic ketoacidosis; SGLT2i, sodium/glucose cotransporter 2 inhibitor.
[a]Spironolactone has little effect on calcium reabsorption.
[b]Amiloride and triamterene are associated with water excretion, whereas spironolactone and eplerenone are associated with water retention.
[c]Translocational hyponatremia and hyperkalemia may occur during drug infusion, whereas hypernatremia and hypokalemia may occur during diuresis.

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Thiazide Diuretics

Thiazides block NCC in the distal convoluted tubule (DCT). This class of diuretics includes the benzothiadiazine derivatives HCTZ and chlorothiazide as well as the thiazide-like diuretics chlorthalidone, metolazone, and indapamide. As the DCT normally reabsorbs only 5%-10% of the filtered sodium load, thiazides by themselves are relatively weak diuretics.

Thiazides significantly decrease BP, an effect caused by natriuresis and vasodilation. Similarly to loop diuretics, thiazides produce hypokalemia, hyperuricemia, and metabolic alkalosis, but hypokalemia is more common with thiazides. Thiazides inhibit a "potassium switch" in the distal nephron, which plays an essential role in potassium reabsorption by the kidneys. Thiazides also increase calcium reabsorption (1) in the proximal tubule from volume contraction and (2) in the DCT from increased basolateral sodium/calcium exchange and luminal calcium influx (Fig 4). Conversely, thiazides decrease magnesium reabsorption in the DCT, possibly by blocking the luminal magnesium channel and the basolateral adenosine triphosphatase sodium/potassium pump

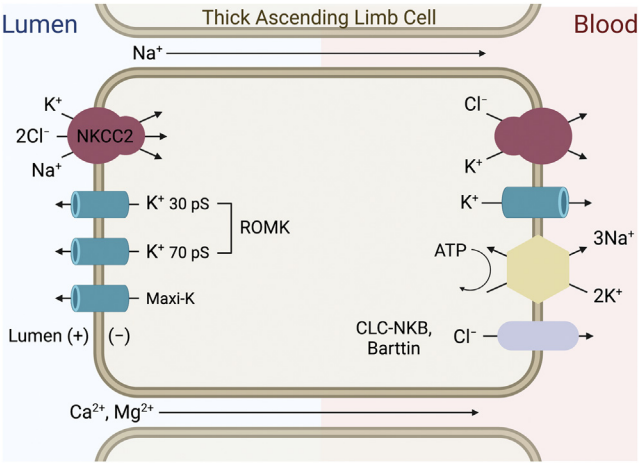

Figure 3. Paracellular calcium and magnesium absorption in the thick ascending limb of the loop of Henle. Loop diuretics block the sodium/potassium/chloride cotransporter. Abbreviations: CLC-NKB, chloride channel; NKCC2, sodium/potassium/chloride cotransporter; ROMK, renal outer medullary potassium channel. Based on information in Mount, 2014 (*Clin J Am Soc Nephrol.* https://doi.org/10.2215/cjn.04480413). Image created with BioRender.

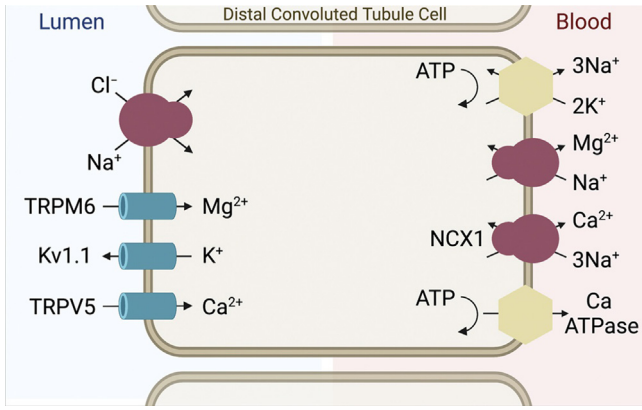

Figure 4. Transcellular calcium and magnesium absorption in the distal convoluted tubule. Abbreviations: Kv1.1, voltage-gated K channel; NCX1, sodium/calcium exchanger; TRPM6, transient receptor potential melastatin 6 Mg channel; TRPV5, transient receptor potential vanilloid 5 Ca channel. Based on information in Blaine et al, 2015 (*Clin J Am Soc Nephrol.* https://doi.org/10.2215/cjn.09750913). Image created with BioRender.

(Na^+/K^+-ATPase). Hyponatremia from these drugs has been attributed to sodium depletion, antidiuretic hormone release, and preexisting prostaglandin receptor polymorphisms. Finally, hyperglycemia from thiazides may be caused by hypokalemia-mediated inhibition of insulin release.

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CAIs

CAs are widely expressed across kingdoms of living organisms and within many tissues, so CAIs are useful in treating disorders other than volume overload (eg, seizures, glaucoma, altitude sickness, obesity, and cancer). In the kidneys, 95% of CA is intracellular CA-II and 5% is membrane-bound CA-IV, and both isoforms are expressed in proximal tubule cells and α-intercalated cells, among others. The best-known CAI is the sulfonamide acetazolamide, but CAIs may derive from other drug classes (eg, phenols, polyamines, thiazides, and coumarins) and include medications such as anticonvulsant agents (eg, topiramate, lacosamide, zonisamide). Proximal sodium wasting is attenuated by distal sodium reabsorption, so CAIs have limited diuretic potency (Fig 5).

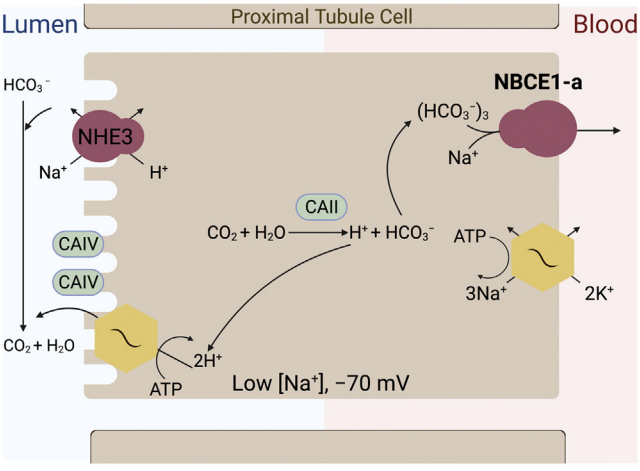

Figure 5. Carbonic anhydrase (CA) in the proximal tubule. Inhibition of CA-IV blocks production of intracellular hydrogen ions, which inhibits NHE3 and causes excretion of sodium ions. Inhibition of CA-II blocks consumption of luminal bicarbonate (HCO_3^-), which is excreted as sodium bicarbonate ($NaHCO_3$). Abbreviations: NHE3, sodium/hydrogen exchanger; NBCE1-a, sodium/bicarbonate cotransporter. Based on information in Hamm et al, 2015 (*Clin J Am Soc Nephrol*. https://doi.org/10.2215/cjn.07400715). Image created with BioRender.

As with the other sulfonamides, CAIs may cause hypovolemia and hypokalemia by increasing sodium excretion. Of the total filtered load, 60%-70% of calcium and 10%-25% of magnesium is reabsorbed by the proximal tubule, so CAIs may also precipitate hypocalcemia or hypomagnesemia. However, the unique property of CAIs is bicarbonate excretion, resulting in urinary alkalinization and metabolic acidosis. Hypercalciuria and alkalinuria, as well as hypocitraturia caused by intracellular acidosis, favor the formation of calcium phosphate stones in 10% of patients receiving CAIs.

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Potassium-Sparing Diuretics

The potassium-sparing diuretics include 2 drug classes, epithelial sodium channel (ENaC) blockers and mineralocorticoid receptor antagonists (MRAs). The ENaC blockers, amiloride and triamterene, block sodium entry into the principal cell, generating a weak diuresis. Critically, ENaC inhibition disrupts the normal lumen-negative potential in the collecting duct, inhibiting potassium and hydrogen ion secretion and promoting calcium and magnesium reabsorption.

The MRAs include, in order of increasing mineralocorticoid receptor selectivity, spironolactone, eplerenone, and finerenone. Finerenone is the first of a new class of nonsteroidal MRAs. Unlike most other diuretics, these steroid hormone inhibitors reach their site of action by basolateral diffusion rather than luminal secretion. As with ENaC blockers, MRAs act in the principal cell, blocking aldosterone-stimulated ENaC, ROMK, and Na^+/K^+-ATPase activity. Similarly, these drugs are weak diuretics and also

cause potassium, magnesium, and hydrogen ion retention, although calcium handling is unaffected. Antiandrogen side effects are greatest with spironolactone and include gynecomastia, dysmenorrhea, and impotence. MRAs are useful in managing hypertension, CHF, and CKD, in part by decreasing inflammation and fibrosis. Finerenone was recently approved by the FDA to decrease the risk of CKD progression and cardiovascular events in patients with diabetic kidney disease.

The patient in case 2 requires ongoing diuresis but has developed hyperkalemia and metabolic alkalosis. Increasing the dose of furosemide or prescribing chlorthalidone would worsen metabolic alkalosis, whereas prescribing spironolactone would worsen hyperkalemia. Prescribing sodium zirconium cyclosilicate, a potassium binder with a high sodium content, would decrease the serum potassium level but could exacerbate volume overload. Prescribing acetazolamide would increase sodium, potassium, and bicarbonate excretion, improving hypervolemia, hyperkalemia, and metabolic alkalosis, respectively. Thus, the answer to question 3 is (d).

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Sodium/Glucose Cotransporter 2 Inhibitors

Sodium/glucose cotransporter 2 (SGLT2) inhibitors reduce sodium and glucose reabsorption from the proximal tubule. Originally developed as hypoglycemic agents, SGLT2 inhibitors have pleiotropic physiological benefits, including decreased inflammation and mild diuresis. Like other drug classes that cause functional decreases in GFR, such as angiotensin-converting enzyme inhibitors, SGLT2 inhibitors acutely reduce GFR by restoring tubuloglomerular feedback but preserve kidney function with long-term use, possibly by attenuating glomerular hypertension. SGLT2 inhibitors improve clinical outcomes, such as slowing the progression of diabetic and nondiabetic CKD and decreasing the risk of AKI, CHF hospitalization, and cardiovascular mortality. Improved heart failure outcomes seem unlikely to be attributable solely to diuresis, but SGLT2 inhibitors may help with decongestion; alternatively, SGLT2 inhibitors may confer benefit by mimicking fasting physiology through adaptive cellular reprogramming. Although guidelines are still evolving regarding the use of these drugs, decreasing the dose of other diuretics may be reasonable when prescribing SGLT2 inhibitors to patients with euvolemia. Other effects of SGTL2 inhibitors include uricosuria, genital and urinary tract infection, and euglycemic diabetic ketoacidosis.

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Vasopressin Receptor Antagonists

Although diuretics agents are traditionally natriuretic drugs, vasopressin receptor antagonists (VRAs) are aquaretic agents, which increase free water excretion. These agents, such as tolvaptan and conivaptan, are inverse agonists at the vasopressin V_2 receptor in the collecting duct. VRAs were designed to manage hyponatremia associated with the syndrome of inappropriate antidiuretic hormone, ESLD, and CHF. In patients with CHF, tolvaptan acutely increases serum sodium and decreases body weight but does not improve long-term CHF morbidity or mortality. Tolvaptan caused a nonsignificant increased risk of GI bleeding in one trial of patients with ESLD, and conivaptan also blocks splanchnic V_1 receptors, theoretically aggravating variceal dilation and bleeding. Finally, in the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3:4 trial, 1,445 patients with early-stage CKD randomized to receive tolvaptan versus placebo showed an increased risk of liver aminotransferase level increase (0.9% vs 0.4%, respectively). For these reasons, the FDA limits VRA therapy for hyponatremia to 30 days and recommends against their use in ESLD. VRA-mediated free water excretion causes polyuria, thirst, and ultimately hypernatremia, as well as hypokalemia from increased

urine flow. The role of VRAs in patients with volume overload requires further study.

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Osmotic Diuretics

Osmotic diuretics are distinct from the others in that they do not act at specific transporters or receptors. These agents, such as mannitol and urea, are freely filtered at the glomerulus and remain in the tubular lumen, reversing the usual 3-5 mOsm/kg H_2O lumen-to-interstitium osmotic pressure difference. Iso-osmotic water and electrolyte reabsorption is inhibited in water-permeable nephron segments, such as the proximal tubule and thin descending limb of the loop of Henle, disrupting countercurrent exchange and the medullary concentration gradient. Moreover, membrane-impermeable agents (ie, effective osmoles) cause cellular dehydration and intravascular volume expansion upon entry into the bloodstream, with electrolyte changes (hyponatremia, hyperkalemia) that may reverse when diuresis has occurred (hypernatremia, hypokalemia). This initial volume expansion may be severe enough to cause pulmonary edema in the case of rapid mannitol infusion. Because of these time-varying effects on volume status, osmotic diuretics are not used to manage volume overload, but are useful for decreasing intracranial pressure in cerebral edema (mannitol) and increasing free water excretion in hyponatremia (urea).

Table 3. Stepwise Diuretic Dosing Algorithm From CARRESS-HF

Level	Furosemide Dose		Suggested Metolazone Dose
	Current	Suggested (Bolus, Infusion)	
A	≤80 mg/d	40 mg, 5 mg/h	0
B	81-160 mg/d	80 mg, 10 mg/h	5 mg/d
C	161-240 mg/d	80 mg, 20 mg/h	5 mg 2×/d
D	≥240 mg/d	80 mg, 30 mg/h	5 mg 2×/d

Therapy was escalated to the next level if 3 L/d urine output was not achieved; other medical and technical interventions were also allowed. Based on information in Bart et al, 2012 (*J Card Fail*. https://doi.org/10.1016/j.cardfail.2011.12.009).
Abbreviation: CARRESS-HF, Cardiorenal Rescue Study in Acute Decompensated Heart Failure.

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Managing Volume Overload and Diuretic Resistance

Heart Failure

As reviewed in cases 1 and 2, loop diuretic agents are the workhorses for decongestion in CHF. Upon hospital admission for ADHF, loop diuretics are usually given IV and at higher doses, such as per the algorithm from the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF; Table 3). This trial included patients with ADHF and AKI and targeted 3-5 L/d urine output. The Diuretic Optimization Strategies Evaluation (DOSE) trial confirmed that patients receiving more furosemide (2.5 times the home dose) compared with those receiving the home dose given IV experienced more weight loss and dyspnea relief, and that twice-daily administration performed as well as continuous infusion. Despite the latter finding, some clinicians prefer continuous infusion to twice-daily administration, especially when frequent dose changes may be desired because of clinical instability. Although torsemide or bumetanide have been touted as superior to furosemide because of better bioavailability, and, in the case of torsemide, longer $t_{1/2}$, clinical trials demonstrating improved readmission rates and symptom scores did not routinely allocate patients to bioequivalent diuretic doses, and mortality benefits have been contested. Interestingly, spontaneous Scr increases from ADHF are associated with increased mortality and more frequent hospital readmission, whereas iatrogenic increases in Scr from successful diuresis are associated with decreased mortality, as long as decongestion is occurring.

Resistance to diuresis may follow from any of the causes in Box 1. The braking phenomenon occurs when the kidneys' initially robust natriuretic response wanes as extracellular fluid volume decreases. This phenomenon has been attributed to RAS activation by CHF and extracellular fluid volume depletion, stimulating sodium reabsorption throughout the nephron, in conjunction

with distal tubule hypertrophy or remodeling, whereby long-term NKCC2 blockade in the loop of Henle causes NCC upregulation in the DCT. Consequently, thiazides may be added to maximal doses of loop diuretics (ie, furosemide 160-320 mg/d IV) to augment urine output. All thiazides seem equally efficacious, and their long $t_{1/2}$ makes timing of their administration with loop diuretic agents unnecessary (ie, 30 minutes before).

As previously mentioned, and separate from decongestion, add-on therapy with dapagliflozin and spironolactone or eplerenone improves morbidity and mortality in patients with systolic CHF. Similarly, VRAs and CAIs are reasonable additions in patients with refractory hyponatremia or metabolic alkalosis, respectively, but their long-term benefits are unproven. Tolvaptan, specifically, has been studied in numerous randomized controlled trials in patients with CHF, and, even though findings are inconclusive, post hoc analysis of 2 of the largest trials has shown improved outcomes in patients with serum sodium levels <130 mEq/L. Vaptans are currently under investigation as adjunctive agents to first-line diuretic agents. Although more data are needed, isolated ultrafiltration has been linked to more frequent adverse events without more weight loss compared with IV furosemide. Compared with furosemide alone, hypertonic saline solution plus furosemide has been reported to improve diuresis, hospital readmission, kidney function, and mortality, but this approach has not been tested in rigorous clinical trials.

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End-Stage Liver Disease

Case 3: *A 57-year-old man with ESLD is admitted to the hospital with worsening ascites and dyspnea. He has a history of hepatitis C, esophageal varices, and CKD G3bA1. He is adherent to prescribed medications, including furosemide, spironolactone, and propranolol. BP is 102/58 mm Hg and heart rate 90 beats per minute. Physical examination reveals a tense, distended abdomen with dullness to percussion at both flanks. His lungs are clear, and there is no peripheral edema. Admission laboratory data include serum sodium level of 130 mEq/L, serum urea nitrogen level of 41 mg/dL, Scr of 1.7 mg/dL (at baseline), and urine sodium level <10 mEq/L.*

Question 4: Which of the following is the next best step in management?

a) Albumin
b) Conivaptan
c) IV furosemide
d) Hydrochlorothiazide
e) Paracentesis

For the answer to the question, see the following text.

Guidelines recommend managing ascites in a stepwise manner based on severity, starting with minimizing ongoing liver damage and restricting sodium intake to <2 g/d. MRAs are considered among the most effective diuretics in ESLD, possibly because they (1) sidestep bile acid– and free fatty acid–mediated inhibition of organic anion (ie, sulfonamide) transport and (2) directly antagonize increased RAS activity. Loop diuretics are often coadministered with MRAs to increase efficacy. Starting prescriptions of spironolactone 50-200 mg/d and furosemide 40-160 mg/d, with titration every 3-4 days, is recommended to target net fluid loss of 1 L/d in patients with edema or 0.5 L/d in those without edema. A standard initial regimen is furosemide 40 mg and spironolactone 100 mg, with progressive titration at the

same ratio. Aggressive diuresis in patients without edema risks intravascular volume depletion and AKI because only 0.4 L/d ascites may be mobilized into the systemic circulation. Patients with refractory ascites (<1.5 kg weight loss per week while receiving dietary sodium <2 g/d and maximally tolerated doses of diuretics) require large-volume paracentesis, transjugular intrahepatic portosystemic shunt creation, or liver transplant.

The patient in case 3 presents with severe (grade 3) ascites while taking oral diuretics and should undergo paracentesis. Albumin is infused during large-volume paracentesis to maintain intravascular volume but, by itself, would likely worsen volume overload. As mentioned, attempting to increase diuresis by prescribing IV furosemide or HCTZ would risk AKI in a patient without peripheral edema. Conivaptan may improve hyponatremia but would not increase natriuresis and may be associated with adverse events such as variceal bleeding in ESLD. The correct answer to question 4 is (e).

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CKD

Case 4: *A 60-year-old woman with CKD G5A3 attributed to type 2 diabetes began thrice-weekly hemodialysis 2 months earlier. Diabetes has been complicated by retinopathy, foot ulcers, peripheral vascular disease, and autonomic neuropathy. The dialysis prescription includes a blood flow rate of 500 mL/min, dialysate flow rate of 500 mL/min, time of 3.5 hours, and dry weight of 48 kg. Single-pool Kt/V averages 1.3, and 24-hour urine volume is 0.9 L. Although the patient has restricted salt and fluid intake, she has been unable to achieve her dry weight because of intradialytic hypotension (IDH); systolic BP usually decreases from 160 to 90 mm Hg during dialysis and is accompanied by cramping and nausea when ultrafiltration exceeds 1 L. Currently, predialysis BP is 158/92 mm Hg and heart rate 78 beats per minute. Physical examination reveals faint bilateral crackles, pitting edema (2+), a stage 1 first metatarsal ulcer, and a functioning arteriovenous graft.*

Question 5: Which of the following is the next best step in management?

a) Increase dialysis time
b) Increase dry weight
c) Prescribe midodrine
d) Prescribe torsemide
e) Change to peritoneal dialysis

For the answer to the question, see the following text.

As CKD progresses, maintaining euvolemia requires excreting the same sodium load with fewer nephrons. This problem is exacerbated by systemic and intrarenal RAS activation, which limits salt excretion. Volume overload in CKD is generally treated by decreasing dietary sodium intake and increasing urinary sodium excretion with loop diuretic. Again, the diuretic response in CKD is blunted by many of the problems listed in Box 1. The luminal concentration of loop diuretics in patients with stage 5 CKD is only 10%-20% of that in individuals with normal kidney function, so diuretic dose must be increased in advanced CKD. Although thiazides were previously thought to be ineffective at GFRs <30 mL/min/1.73 m^2, recent evidence suggests that chlorthalidone, specifically, may be an effective antihypertensive and second-line diuretic in stage 4 CKD.

Diuretics may benefit patients receiving dialysis who have residual kidney function. In patients undergoing thrice-weekly hemodialysis, high interdialytic weight gain necessitates a high ultrafiltration rate, which is frequently complicated by IDH and predicts cardiovascular events and death. Conversely, loop diuretic use is associated with decreased interdialytic weight gain and less frequent IDH and hospitalization. Although peritoneal dialysis allows continuous ultrafiltration, volume overload is common, and diuretics help minimize the use of high-dextrose dialysates that may damage the peritoneal membrane.

Euvolemia cannot be achieved in the patient in case 4 because of IDH. Increasing dialysis time within reasonable constraints is unlikely to mitigate IDH. Increasing dry weight would lessen IDH but worsen volume overload. Midodrine, an α_1-adrenergic agonist, is frequently used to manage IDH but may worsen clinical outcomes. Changing from hemodialysis to peritoneal dialysis may improve volume status, but modality choice involves personal, logistical, and surgical considerations and would not be the next best step in management. This patient should initially take a loop diuretic to manage hypervolemia and IDH, so the correct answer to question 5 is (d).

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Nephrotic Syndrome

Case 5: *A 24-year-old woman presents to the clinic for ongoing management of nephrotic syndrome from minimal change disease. She initially presented 3 months earlier with edema, proteinuria, and hypoalbuminemia and was prescribed lisinopril and furosemide. Following kidney biopsy 2 months earlier, prednisone, omeprazole, and trimethoprim-sulfamethoxazole were added. During the previous 3 months, urinary protein-creatinine ratio has improved from 7.8 to 3.3 g/d and weight has decreased from 84 to 75 kg, but serum magnesium level has remained low despite aggressive oral supplementation with magnesium oxide. BP is 138/78 mm Hg and heart rate 88 beats per minute. Physical examination is significant for pitting edema (1+). Laboratory data include serum sodium level of 139 mEq/L, potassium level of 3.9 mEq/L, calcium level of 8.9 mg/dL, magnesium level of 1.2 mg/dL, serum urea nitrogen level of 23 mg/dL, and Scr of 0.9 mg/dL (stable); urine sodium level is 82 mEq/L, magnesium level is 29 mg/dL, and creatinine level is 121 mg/dL.*

Question 6: Which of the following is the next best step in managing hypomagnesemia?

a) Prescribe IV magnesium chloride
b) Prescribe chlorthalidone
c) Prescribe amiloride
d) Discontinue furosemide
e) Discontinue omeprazole

For the answer to the question, see the following text.

Nephrotic syndrome is characterized by nephrotic-range proteinuria (>3.5 g/d), hypoalbuminemia, peripheral edema, and often hyperlipidemia and hypercoagulability. The genesis of edema has been attributed to "underfill," in which hypoalbuminemia reduces the oncotic pressure gradient from serum to interstitium, or "overfill," in which the nephrotic kidneys retain sodium and water. The underfill hypothesis has been criticized because the required oncotic pressure gradient cannot be demonstrated consistently; indeed, as serum albumin level decreases, interstitial albumin level tends to decrease in parallel because of dilution and lymphatic equilibration. Conversely, the overfill hypothesis has become increasingly attractive based on experimental and clinical validation of the following sequence of events: heavy urinary filtration of plasminogen with urokinase-mediated conversion to plasmin causes proteolytic cleavage of the ENaC γ-subunit, constitutive ENaC activation, and unregulated sodium reabsorption. Increased sympathetic nervous system activity, decreased response to atrial natriuretic peptide, and abnormal expression of acid-sensing ion channel 2 may also contribute to sodium retention. However, the observation that primary renal sodium retention causes hypertension rather than edema as a result of pressure natriuresis suggests that nephrotic edema may reflect a mixture of underfill and overfill pathophysiology. Some patients appear to exhibit decreased effective arterial blood volume, especially children with minimal change disease.

As in most hypervolemic states, loop diuretics are essential in managing nephrotic edema. Diuretic resistance may be attributable to decreased absorption from GI tract edema, decreased delivery from hypoalbuminemia, and decreased secretion from intrarenal edema ("nephrosarca"). Based on overfill pathophysiology, ENaC blockers may be useful adjuncts to loop diuretics for volume management, even though clinical evidence is scarce. Other diuretics, including thiazides and CAIs, have also been effective in managing nephrotic edema.

In case 5, proteinuria and edema are responding to immunosuppression, RAS blockade, and diuresis, but hypervolemia and hypomagnesemia remain. The fractional excretion of magnesium is 18%, indicating renal magnesium wasting; thus, discontinuing omeprazole, which would address GI magnesium wasting, would not be useful. Similarly, changing from oral to IV magnesium supplementation would not be expected to improve hypomagnesemia while renal losses continue. Hypermagnesuria is almost certainly caused by furosemide-mediated diuresis, but discontinuing this diuretic could worsen volume overload while proteinuria persists. Chlorthalidone and amiloride would both augment diuresis, but only amiloride would increase magnesium retention. The answer to question 6 is therefore (c).

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