AJKD

Acid-Base and Electrolyte Teaching Case

Diuretic Resistance

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Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic. The causes of diuretic resistance include poor adherence to drug therapy or dietary sodium restriction, pharmacokinetic issues, and compensatory increases in sodium reabsorption in nephron sites that are not blocked by the diuretic. To illustrate the pathophysiology and management of diuretic resistance, we describe a patient with nephrotic syndrome. This patient presented with generalized pitting edema and weight gain despite the use of oral loop diuretics. Nephrotic syndrome may cause mucosal edema of the intestine, limiting the absorption of diuretics. In addition, the patient's kidney function had deteriorated, impairing the tubular secretion of diuretics. He was admitted for intravenous loop diuretic treatment. However, this was ineffective, likely due to compensatory sodium reabsorption by other tubular segments. The combination of loop diuretics with triamterene, a blocker of the epithelial sodium channel, effectively reduced body weight and edema. Recent data suggest that plasmin in nephrotic urine can activate the epithelial sodium channel, potentially contributing to the diuretic resistance in this patient. This case is used to illustrate and review the mechanisms of, and possible interventions for, diuretic resistance.

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INDEX WORDS: Diuretic resistance; pathophysiology; edema; oral loop diuretic; nephrotic syndrome; triamterene; eNaC; epithelial Na^+ channel; *SCNN1B*; proteinuria; kidney disease; cryoglobulinemic membranoproliferative glomerulonephritis; hepatitis C virus.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting the diagnosis and treatment of acid-base and electrolyte disorders.

INTRODUCTION

Generalized edema can develop in nephrotic syndrome, chronic kidney disease (CKD), heart failure, and liver cirrhosis. Usually patients with edema respond to dietary sodium restriction in combination with a loop diuretic.[1] However, some patients become resistant to diuretics. Diuretic resistance is defined as failure to achieve the therapeutically desired reduction in edema even when a maximal dose of diuretic is employed. Box 1 summarizes the main causes of diuretic resistance,[2] which include poor adherence to diet or drug therapy, pharmacokinetic issues, and compensatory increases in sodium reabsorption in nephron sites that are not blocked by the diuretic.[3] Establishing the cause of diuretic resistance is important because it directly informs the options for intervention. For example, diuretic resistance is often treated effectively by combining a loop diuretic with another type of diuretic.[4] We present a patient to illustrate the causes, pathophysiologic mechanisms, and treatment of diuretic resistance.

CASE REPORT

Clinical History and Initial Laboratory Data

A 55-year-old man was admitted because of edema and dyspnea. He had a history of chronic hepatitis C virus infection (genotype 1A) without evidence for liver cirrhosis (no fibrosis or portal hypertension on ultrasound and no fibrosis on elastography). Secondary to hepatitis C virus infection, he developed membranoproliferative glomerulonephritis with 2 episodes of nephrotic syndrome. These episodes of nephrotic syndrome resolved after treatment with a combination of glucocorticoids and loop diuretics, but resulted in progressive glomerular filtration rate (GFR) loss. His estimated GFR prior to admission was 37 mL/min/1.73 m^2 (as calculated by the CKD-EPI [CKD Epidemiology Collaboration] equation[5]). His outpatient medication consisted of bumetanide (1 mg 2 times daily), losartan (25 mg once daily), and spironolactone (25 mg once daily). At presentation, he was alert but was concerned about edema and dyspnea. On physical examination, blood pressure was 145/110 mm Hg, while his body weight had increased by 20 kg. He had ascites, but his liver was not enlarged. Generalized pitting edema reaching up to his scrotum was present. Based on the presence of edema and his laboratory results, the recurrence of nephrotic syndrome was established (Table 1).

Additional Investigations

A kidney biopsy was performed (42 glomeruli, 18 with global sclerosis). Light microscopy showed thickened glomerular

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Box 1. Common Causes of Diuretic Resistance

- Incorrect diagnosis (eg, venous or lymphatic edema)
- Nonadherence to recommended sodium and/or fluid restriction
- Drug not reaching the kidney
  - ◇ Nonadherence
  - ◇ Dose too low or too infrequent
  - ◇ Poor absorption
- Reduced diuretic secretion
  - ◇ Tubular uptake of diuretic impaired by uremic toxins
  - ◇ Decreased kidney blood flow
  - ◇ Decreased functional kidney mass
- Insufficient kidney response to drug
  - ◇ Low glomerular filtration rate
  - ◇ Decreased effective intravascular volume despite elevated total extracellular fluid volume
  - ◇ Activation of the renin-angiotensin system
  - ◇ Nephron adaptation
  - ◇ Use of nonsteroidal anti-inflammatory drugs

Based on Hoorn et al.[2]

basement membrane and increased mesangial and endocapillary cellularity. Immunofluorescence showed positivity for immunoglobulin G (IgG), IgM, C3, and κ and λ light chains in a granular pattern. Electron microscopy was not performed.

Diagnosis

Diuretic resistance caused by the recurrence of nephrotic syndrome secondary to hepatitis C virus–related cryoglobulinemic membranoproliferative glomerulonephritis.

Clinical Follow-up

The patient was admitted for intravenous loop diuretic treatment with a continuous infusion of 10 mg/d of bumetanide (Fig 1). Despite this treatment, he did not lose weight and therefore a thiazide type diuretic (chlorthalidone) was added after the first week. Because this combination also failed to lower his body weight, loop diuretics were combined with the epithelial sodium channel (ENaC) blocker triamterene (100 mg/d). In addition, he was treated with rituximab (1 g intravenously in weeks 2 and 3 of admission) because of the recurrence of membranoproliferative glomerulonephritis secondary to hepatitis C virus infection. The combination of diuretics and B-cell depletion therapy resulted in resolution of edema, an increase in serum albumin level to 2.7 g/dL, a reduction in body weight, and an improvement in kidney function. However, proteinuria was largely unchanged, in the nephrotic range (protein excretion, 10 g/d). Although interferon-free therapy was not available during the treatment of this patient, he is currently treated with sofosbuvir and daclatasvir.

Table 1. Laboratory Data

Parameter	Value	Reference Range
Serum chemistry		
Sodium, mEq/L	141	136-145
Potassium, mEq/L	5.4	3.5-5.1
Creatinine, mg/dL	3.9	0.74-1.3
eGFR, mL/min/1.73 m^2	16	
Albumin, g/dL	1.8	3.5-5.0
Cryoglobulins, g/L	0.02	<0.01
Urine chemistry		
Protein, g/d	14	<0.14
Sodium, mEq/d	9	-

Note: Conversion factor for creatinine in mg/dL to μmol/L, ×88.4.

Abbreviation: eGFR, estimated glomerular filtration rate.

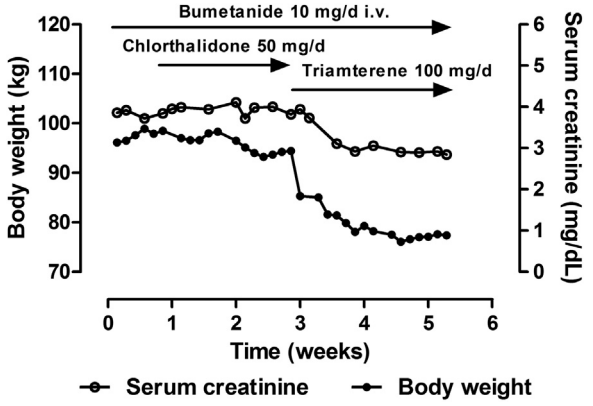

Figure 1. Patient's course in terms of body weight and serum creatinine levels during admission. Treatment periods with diuretics are indicated. Abbreviation: i.v., intravenous. Conversion factor for creatinine in mg/dL to μmol/L, ×88.4.

DISCUSSION

This case illustrates several of the possible causes of diuretic resistance and strategies to overcome it. In addition to discussing diuretic resistance in this specific patient with nephrotic syndrome, we also discuss mechanisms pertaining to diuretic resistance in CKD, heart failure, and liver cirrhosis.

There are several classes of diuretics, dictated by their site of action in the nephron (Fig 2).[2] They include diuretics that act on the proximal tubule, carbonic anhydrase inhibitors; loop of Henle, loop diuretics; distal tubule, thiazide diuretics; or collecting duct, distal potassium-sparing diuretics. Distal potassium-sparing diuretics can be further subdivided into either ENaC blockers or mineralocorticoid receptor blockers (eg, spironolactone or eplerenone). Except for mineralocorticoid receptor blockers, diuretics act from the tubular lumen by blocking the function of sodium transport proteins in the apical plasma membrane of kidney epithelial cells. This implies that for these diuretics to act, they must first be secreted in tubular fluid. Thus, diuretics are delivered to their site of action by tubular secretion rather than glomerular filtration. Tubular secretion of diuretics primarily occurs in the proximal tubule. For most diuretics, the secretory pathways have largely been identified and involve organic anion transporters and multidrug resistance proteins.[6] The importance of this secretory process is illustrated by the observation that decreased diuretic secretion into the tubular lumen is often one of the causes of diuretic resistance (Box 1).

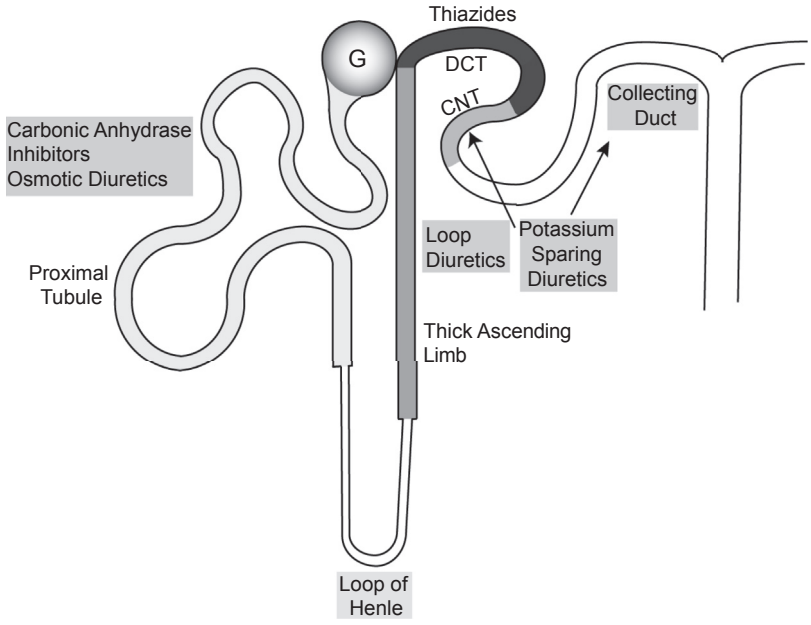

Figure 2. Schematic of a nephron shows sites of action of diuretics along the various segments. Abbreviations: CNT, connecting tubule; DCT, distal convoluted tubule; G, glomerulus.

Both pharmacokinetic and pharmacodynamic effects may contribute to diuretic resistance and may arise at any level of the drug absorption and delivery process (Table 2).[7,8] For example, nephrotic syndrome may cause mucosal edema of the intestine, thereby limiting the absorption of oral diuretics.[9] This may also play a role in patients with heart failure or liver cirrhosis, although in these conditions, decreased intestinal perfusion and reduced intestinal motility are more likely to limit absorption. Even in the absence of these factors, there is a remarkable difference in bioavailability between the different types of loop diuretics. For example, the bioavailability of furosemide (40%-60%) is much lower compared to bumetanide (80%) or torsemide (>91%).[10,11] When an adequate plasma concentration of the diuretic is achieved, it must be secreted adequately into the tubule lumen. This process is frequently compromised in edematous disorders. In nephrotic syndrome, hypoalbuminemia may reduce the delivery of diuretic to the kidney tubule because loop diuretics are highly protein bound. Experimental animal models of nephrotic syndrome suggested that urinary albumin could also bind furosemide after it had been secreted.[12] However, a study of patients with nephrotic syndrome in which loop diuretics were combined with the displacing agent sulfisoxazole was unable to confirm this mechanism.[13] The effects of adding salt-poor human albumin to intravenous loop diuretics are modest and vary per study.[14,15] Because it may also have an adverse effect, it is recommended to reserve this treatment for patients with refractory anasarca with respiratory compromise or tissue damage.[16] In CKD, the secretion of diuretics may be inhibited by retained organic anions, uric acid, or acidosis.[17] Because our patient had both nephrotic syndrome and CKD, both mechanisms may have contributed to diuretic resistance. In heart failure or liver cirrhosis, the primary mechanism limiting diuretic secretion is usually vasoconstriction of kidney blood vessels due to reduced cardiac output or splanchnic vasodilation, respectively. In patients with heart failure, the dose-response curve for loop diuretics (fractional sodium excretion vs plasma furosemide concentration) exhibits both a rightward and a downward shift (secretory defect and decreased maximal response).[2] In contrast, CKD causes only a rightward shift in the dose-response curve.

Table 2. Pharmacokinetics of Loop Diuretics

		Elimination Half-Life, h			
	Bioavailability, % Oral Dose Absorbed	Healthy	Kidney Disease	Liver Disease	Heart Failure
Furosemide	50 (range, 10-100)	1.5-2	2.8	2.5	2.7
Bumetanide	80-100	1	1.6	2.3	1.3
Torsemide	80-100	3-4	4-5	8	6

Data from Shankar and Brater.[7]

This implies that the maximal response is preserved when expressed as fractional sodium excretion, but it is important to emphasize that maximal absolute increase in sodium excretion is reduced in CKD.

In addition to pharmacokinetic effects, compensatory upregulation of sodium transporters not blocked by the diuretic also contributes to diuretic resistance. Why does this occur? Several systemic and more local mechanisms have been implicated. For example, the systemic renin-angiotensin system (RAS) is activated in heart failure and liver cirrhosis[18] and also becomes activated by loop diuretic treatment.[19,20] In patients with CKD, plasma aldosterone levels may be elevated even in the presence of normal plasma renin activity and normal serum potassium concentrations.[21] Elevated plasma levels of both angiotensin II and aldosterone can activate sodium transporters in the distal nephron, including the Na^+/Cl^- cotransporter and ENaC.[20,22] Angiotensin II also stimulates proximal tubular sodium reabsorption, which will reduce distal sodium delivery and contribute to diuretic resistance. It is also becoming increasingly clear that the systemic and the intrarenal RAS may operate independently.[22] In several disorders, including CKD, the intrarenal RAS may be activated, resulting in increased angiotensin II production in the kidney.[23] Although convincing evidence is lacking, it has been proposed that in such circumstances, intratubular angiotensin II can activate sodium transporters through apical angiotensin type 1 receptors.[24] A recent study showed that additional processes, including distal nephron remodeling and paracrine signaling, are also likely involved in the compensatory response to diuretics.[25] In a mouse model of genetic Na^+/Cl^- cotransporter inhibition (mimicking long-term treatment with thiazide diuretics), a jagged 1-NOTCH interaction was shown to expand and remodel the cortical connecting tubule to favor salt reabsorption pathways.[26] Similarly, via paracrine signaling, α-ketoglutarate secretion was observed to increase the activity of ENaC and the chloride/iodide exchanger pendrin in mice with Na^+/Cl^- cotransporter inhibition. These data suggest that Na^+/Cl^- cotransporter inhibition by thiazide diuretics can cause similar compensatory mechanisms downstream that will limit the maximal natriuretic effect.[25]

In patients with nephrotic syndrome, sodium retention does not seem to be mediated by RAS but rather by an "intrarenal defect."[27,28] Clues to what this intrarenal defect might be have recently become clearer. Namely, plasmin in nephrotic urine was shown to activate the sodium transporter ENaC (Fig 3).[29] It was postulated that tubular urokinase-type plasminogen activator converts filtered plasminogen to plasmin.[29] Plasmin may activate ENaC either directly or indirectly through interaction with

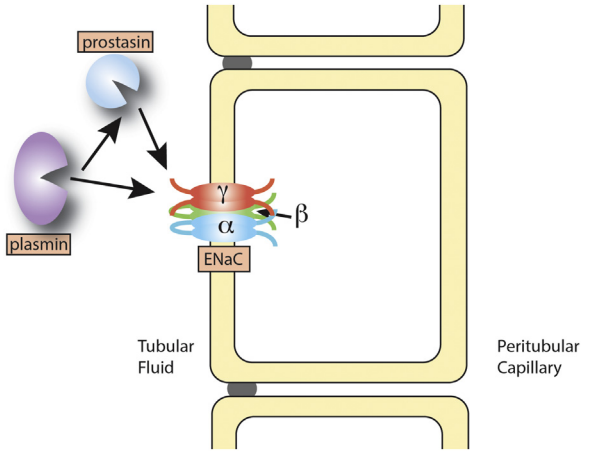

Figure 3. Schematic of proposed mechanism by which luminal plasmin in nephrotic patients activates the epithelial sodium channel (ENaC) in the collecting duct. eNaC comprises 3 subunits, α, β, and γ, each with extracellular loops, as shown. Plasmin, derived from filtered plasminogen in nephrotic patients, cleaves eNaC extracellular loops (γ subunit shown here). Plasmin may also activate prostasin, which can also cleave ENaC. Notches in plasmin and prostasin indicate active enzymatic activity. When cleaved, ENaC is activated, increasing sodium reabsorption. Epithelial cells are shown schematically, separating tubular fluid (lumen) from peritubular capillary.

prostasin and subsequent cleavage of the γ subunit of ENaC.[30] Subsequent studies have indicated that this mechanism could also play a role in sodium retention associated with preeclampsia, resistant hypertension, heart failure, and diabetic nephropathy.[31-34] Of interest, a recent study analyzed whether this mechanism could also play a role in patients with CKD who did not have nephrotic-range proteinuria.[35] To this end, the authors performed a cross-sectional study in 171 outpatients with CKD (different cause and stages and varying degrees of proteinuria) and 2 control groups including healthy volunteers and patients with nephrotic syndrome. The investigators found that proteinuria was the strongest independent predictor for hypervolemia, as assessed by bioimpedance spectroscopy. Plasminuria was found in 44% of patients with CKD (vs 100% in patients with nephrotic syndrome) and predicted hypervolemia similar to proteinuria. In our patient, the prompt decrease in body weight after starting treatment with the ENaC blocker triamterene (in combination with loop diuretics and rituximab) suggests that increased ENaC activity may have contributed to salt and water retention (Fig 1). Moreover, the observation that the marked diuresis preceded the decrease in serum creatinine level suggests that intrarenal edema may have compromised glomerular hemodynamics ("nephrosarca"), as noted previously.[36]

How do these pathophysiologic mechanisms translate into practical strategies to overcome diuretic resistance? An algorithm to guide management is

provided in Fig 4.[37] First, the possibility of nonadherence or the use of nonsteroidal anti-inflammatory drugs should be ruled out (Box 1). In addition, dietary counseling may be indicated to help institute a low-sodium diet. If the patient remains resistant to diuretics, the potential pharmacokinetic causes of diuretic resistance should be addressed by increasing the dose of oral diuretic or by admitting patients for intravenous loop diuretic treatment (as in our case). The type of loop diuretic that is prescribed for oral administration may be relevant, as illustrated by an open-label randomized trial showing fewer readmissions for heart failure with torsemide than with furosemide.[38] When loop diuretics are given

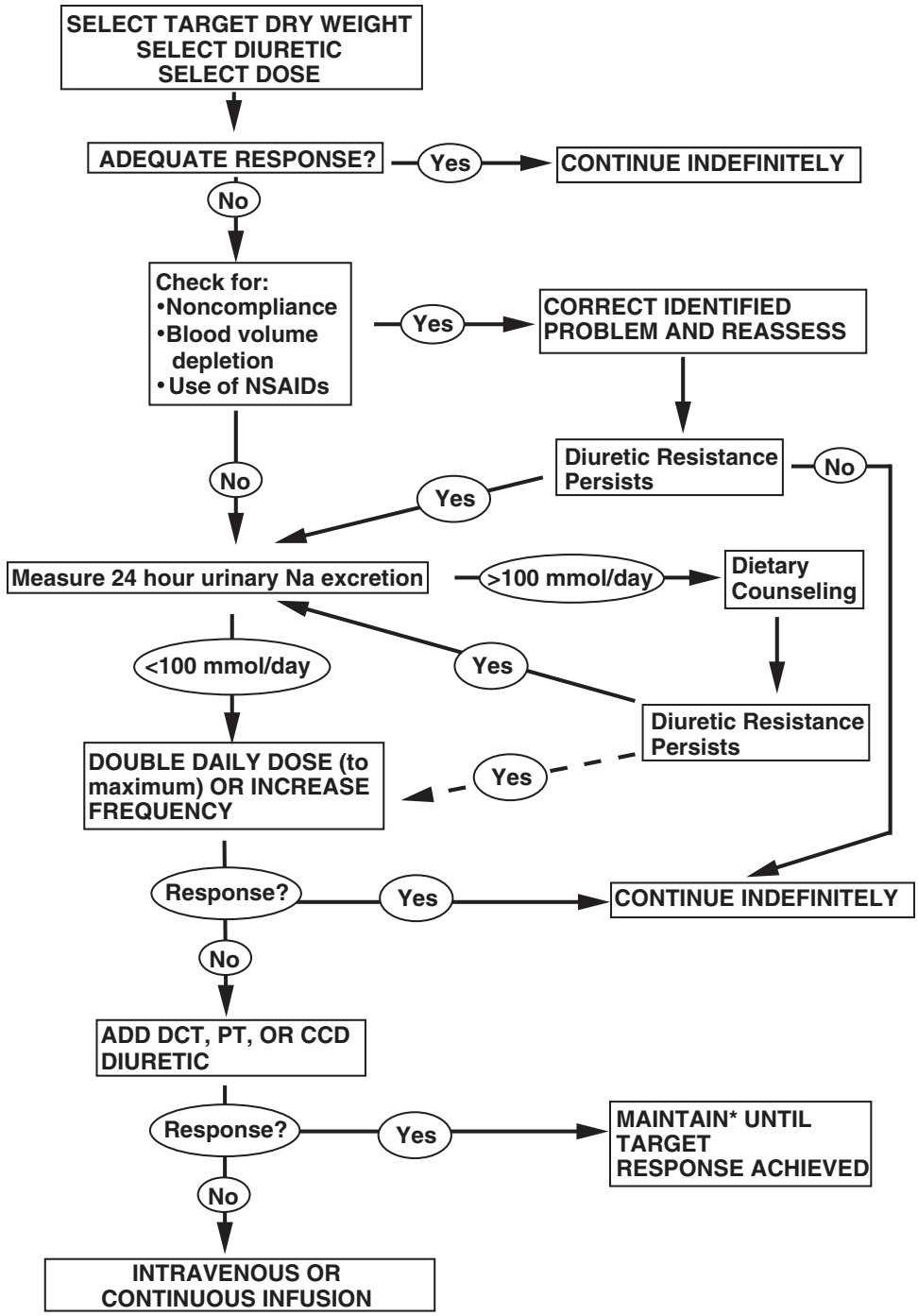

Figure 4. Stepwise approach to assess and manage diuretic resistance. *Consider reducing the dose or frequency of distal convoluted tubule (DCT) diuretic when control of edema has been achieved. Abbreviations: CCD, cortical collecting duct; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, proximal tubule. Adapted from Brady and Wilcox[37] with permission of Elsevier.

intravenously to patients with acute decompensated heart failure, varying the dose or the mode of administration (bolus vs continuous) has been reported by Felker et al[39] to have little impact on symptoms or kidney function. However, the patients enrolled in that study were not characteristic of those with true diuretic resistance because they responded to loop diuretics at traditional doses. A previous smaller study suggested greater urinary volume and sodium excretion and less ototoxicity with continuous than with bolus furosemide infusion.[40]

The key strategy to overcome diuretic resistance in many patients is combining 2 types of diuretics (diuretic synergism).[1] Because loop diuretics are the first drug of choice in edematous disorders, this implies adding a diuretic that targets another tubular segment.[1] Especially for patients with liver cirrhosis and ascites, the specific combination of furosemide and spironolactone is supported by data.[41,42] For the other edematous disorders, the evidence for specific combinations of diuretics is less obvious, and usually a thiazide diuretic is recommended as a second diuretic (as was done in our case).[1] Because kidney function is often reduced in edematous disorders, another recommendation is to titrate the thiazide diuretic according to estimated GFR.[1] Even in patients with severe CKD who are treated with loop diuretics, the addition of a thiazide diuretic can be remarkably effective. For example, in 5 patients with CKD stages 3b to 4 who were using 160 to 240 mg of furosemide per day, the addition of hydrochlorothiazide (50-100 mg/d) markedly reduced body weight, plasma volume, and blood pressure.[43] Similar effects were reported in 9 patients with CKD stages 3b to 4 in whom chlorthalidone (25-100 mg/d) was added to loop diuretic treatment.[44] Given the emerging data on the role of plasmin-induced eNaC activation in proteinuric patients, a relevant but unanswered question is whether it would be more effective to add amiloride instead of a thiazide diuretic.[45] Another new insight is that acetazolamide inhibits pendrin.[46] Because pendrin is increasingly recognized as an important sodium reabsorption route[47,48] and there are no specific inhibitors for pendrin, acetazolamide may be considered as a second diuretic in edematous disorders. In mice, both the coadministration of hydrochlorothiazide and acetazolamide and the double genetic knockout of the Na^+/Cl^- cotransporter and pendrin have been reported to result in severe salt wasting.[46,49] Future studies in patients are necessary to analyze whether the proposed efficacy of amiloride and acetazolamide can be confirmed clinically. If so, this would mean an unexpected reappraisal of these old diuretics. The key teaching points of this review are summarized in Box 2.

Box 2. Key Teaching Points

- Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic
- The causes of diuretic resistance include poor adherence to drug therapy or diet, pharmacokinetic issues, and compensatory sodium reabsorption
- Impaired tubular secretion of diuretics is a common cause of diuretic resistance
- A key strategy to overcome diuretic resistance frequently relies on combining 2 types of diuretic (diuretic synergism)
- In patients with proteinuria, activation of ENaC by plasmin may contribute to salt retention, suggesting efficacy of an ENaC blocker

Abbreviation: ENaC, epithelial sodium channel.

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