Diuretics are among the most commonly prescribed drugs and, although effective, they are often used to treat patients at substantial risk for complications, making it especially important to understand and appreciate their pharmacokinetics and pharmacodynamics (see recent review by Keller and Hann [1]). Although the available diuretic drugs possess distinctive pharmacokinetic and pharmacodynamic properties that affect both response and potential for adverse effects, many clinicians use them in a stereotyped manner, reducing effectiveness and potentially increasing side effects (common diuretic side effects are listed in Table 1). Diuretics have many uses, but this review will focus on diuretics to treat extracellular fluid (ECF) volume expansion and edema; the reader is referred elsewhere for discussion of diuretic treatment of hypertension, kidney stones, and other conditions.

**Classification and Mechanisms of Action**

Diuretic drugs are typically classified first according to their predominant site of action along the nephron and second by the mechanism by which they inhibit transport (Figure 1A). The loop diuretics furosemide, bumetanide, and torsemide act from the lumen to inhibit the Na-K-2Cl cotransporter (NKCC2, encoded by SLC12A1) along the thick ascending limb and macula densa. As organic anions, they bind within the translocation pocket on the transport protein by interacting with the chloride-binding site (2) (Figure 1B, see below for clinical relevance). Because they are larger than chloride, they are not transported through the pocket, and thereby inhibit the transporter. Distal convoluted tubule diuretics (thiazides and thiazide-like drugs) are also organic anions that act in much the same manner, but bind to the thiazide-sensitive NaCl cotransporter (NCC, encoded by SLC12A3) along the distal convoluted tubule (Figure 1A). This mechanism of action accounts for a key aspect of loop and distal convoluted tubule diuretic action; these drugs both exert their effect from the luminal side of the tubule.

Potassium-sparing diuretics include drugs that block apical sodium channels (amiloride and triamterene) and those that antagonize mineralocorticoid receptors (spironolactone and eplerenone). A new nonsteroidal mineralocorticoid blocker, finerenone, is currently in phase 3 clinical trials. The mineralocorticoid blockers and perhaps ethacrynic acid, a more toxic loop diuretic, act within cells and do not require secretion into the tubule lumen.

**Gastrointestinal Absorption of Diuretics**

The normal metabolism of loop diuretics is shown in Figure 2A. Furosemide, bumetanide, and torsemide are absorbed relatively quickly after oral administration (see Figure 2B), reaching peak concentrations within 0.5–2 hours (3,4); when administered intravenously, their effects are nearly instantaneous. The oral bioavailability of bumetanide and torsemide typically exceeds 80%, whereas that of furosemide is substantially lower, at approximately 50% (see Table 2) (5). Although the t1/2 of furosemide is short, its duration of action is longer when administered orally, as its gastrointestinal absorption may be slower than its elimination t1/2. This is a phenomenon called “absorption-limited kinetics” (3) and may explain the mnemonic that this drug “lasts 6 hours” (6). This is not the case for bumetanide and torsemide, where oral absorption is rapid (7). On the basis of oral bioavailability, when a patient is switched from intravenous to oral loop diuretic, the dose of bumetanide or torsemide should be maintained, whereas the dose of furosemide should be doubled (7); in practice, however, and as discussed further below, other factors affect diuretic efficacy, and a fixed intravenous/oral conversion cannot be given (8).

The loop diuretics have steep dose-response curves. This property, although typically taught to students and residents, is often neglected in clinical practice but is crucial to optimal use. Figure 2C shows a typical natriuretic response plotted versus the logarithm of the plasma diuretic concentration. Inspection reveals that there is little diuretic or natriuretic effect below a given plasma concentration (identified as the “threshold”), above which the response increases rapidly. Although such relations are typically plotted as the logarithm of the diuretic concentration or dose, clinicians do not typically “think” in logarithmic terms. This underlies the reasoning behind the common recommendation to “double the dose,” if no response is obtained. At higher concentrations, a plateau or “ceiling” is reached, with progressively higher plasma concentrations failing to elicit more natriuresis. Although this fact has been used to invoke the concept of ceiling doses of loop diuretics, we will argue that increasing a diuretic dose above this ceiling often elicits more natriuresis, owing to pharmacokinetic considerations (see below).

As should be evident from Figure 2C, a diuretic dose must exceed the threshold to be effective; yet the failure to give a dose that exceeds the threshold is one
of the most common errors in diuretic usage. The problem is that the threshold is not easily estimated in an individual, especially an individual with kidney or heart disease. Although nearly all healthy individuals will respond to 20 mg furosemide (or its equivalent), given orally, healthy individuals are not typically treated. As discussed below, conditions that predispose to ECF volume expansion and edema alter both the pharmacokinetics and pharmacodynamics of diuretics. It is little wonder that an empirically selected dose may be ineffective. Below, we will provide broad generalizations about dose adjustments for individuals with a variety of edematous disorders. Yet, adherence to algorithms may lead to diuretic failure. Instead, it is often best to approach a patient as an “n of one trial,” that is, start with a dose consistent with the clinical guidelines (more aggressive for acute edema, more conservative for more chronic processes) and then adjust the dose according to the response.

Although limited bioavailability is a concern with furosemide, a larger problem may be its inconsistent bioavailability. Furosemide absorption varies from day to day in an individual, and between individuals (9,10). Absorption is also affected by food consumption, unlike that of bumetanide or torsemide (11, 12), although the clinical significance of this effect has been doubted (3). The more consistent bioavailability of torsemide, compared with furosemide, and its relatively longer t1/2, have suggested that it may be a superior loop diuretic, as suggested by two small, clinical trials (13–16). A recent post hoc analysis of the large Effect of Nesiritide in Patients with Acute Decompensated Heart Failure study suggested that patients with heart failure discharged on torsemide might have lower mortality (17). Yet, none of these studies is sufficiently powered or rigorous enough to be considered definitive, and some other studies do not suggest such a benefit (18).

Gastrointestinal absorption can be slowed, especially during exacerbations of edematous disorders such as heart failure, although again, this may be true primarily of furosemide (19). Although total bioavailability is typically maintained in these situations, natriuresis may be impaired when absorption is slowed, especially given a concomitant increase in natriuretic threshold, as shown in Figure 2B. As an example, the areas under the curves for arbitrary intravenous and doubled oral furosemide doses may be similar, but the time above the

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**Table 1. Common side effects of diuretics**

<table>
<thead>
<tr>
<th>Loop diuretics</th>
<th>Distal convoluted tubule diuretics</th>
<th>Potassium-sparing diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity reactions</td>
<td>Hypersensitivity reactions</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Extracellular fluid volume depletion</td>
<td>Hyponatremia</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Hypokalemic alkalosis</td>
<td>Hypokalemia</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Hyperglycemia/diabetes</td>
<td>Hyperuricemia/gout</td>
</tr>
<tr>
<td>Otoxicity</td>
<td>Hyperuricemia/gout</td>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia and prerenal azotemia, when combined with loop diuretics</td>
<td>Hypokalemia and prerenal azotemia, when combined with loop diuretics</td>
</tr>
</tbody>
</table>

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**Figure 1. Sites of sodium reabsorption and diuretic action along the nephron.** (A) Nephron figure showing percentages of sodium reabsorption by associated segment. (B) Homology structural model of the loop diuretic–sensitive NKCC2 viewed from the extracellular surface. The pocket for ion translocation and diuretic binding is shown by the arrow. Mutation of a key phenylalanine (F372) alters diuretic binding (reconstruction adapted from Somasekharan et al. [2]). Aldo, aldosterone; Aml, amiloride (and triamterene); CAI, carbonic anhydrase inhibitors; DCTD, distal convoluted tubule diuretic; LD, loop diuretics; MR, mineralocorticoid receptor, site of spironolactone and eplerenone action (not shown).
natriuretic threshold may be different when the natriuretic threshold is increased by disease. This is likely to explain the common observation that intravenous doses of loop diuretics, which achieve higher peak levels, may be effective when oral doses lose their effectiveness, especially if the natriuretic threshold is increased.

Volumes of Distribution, Metabolism, and $t_{1/2}$

Loop diuretics are organic anions that circulate tightly bound to albumin (>95%). Thus, their volumes of distribution are low, except during extreme hypoalbuminemia (20). This has suggested that severe hypoalbuminemia might impair diuretic effectiveness, owing to impaired delivery to

### Table 2. Pharmacokinetics of commonly used diuretics

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Oral Bioavailability, %</th>
<th>Normal $t_{1/2}$, h</th>
<th>CKD $t_{1/2}$, h</th>
<th>Cirrhotic Ascites $t_{1/2}$, h</th>
<th>Heart Failure $t_{1/2}$, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>50 (10–100)</td>
<td>1.5–2</td>
<td>2.8</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>80–100</td>
<td>1</td>
<td>1.6</td>
<td>2.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Torsemide</td>
<td>68–100</td>
<td>3–4</td>
<td>4–5</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>55–77</td>
<td>6–15</td>
<td>Prolonged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>61–72</td>
<td>40–60</td>
<td>Prolonged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metolazone</td>
<td>70–90$^a$</td>
<td>14–20</td>
<td>Prolonged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>$\leq 50^b$</td>
<td>6–26</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>$&gt;90^c$</td>
<td>1.5$^d$</td>
<td></td>
<td>Not changed</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as single reported values or range of reported values. Values for furosemide are given as the mean (range). When precise values were not provided, descriptive terms are provided.

$^a$Absorption may be decreased in heart failure.

$^b$Decreased by food.

$^c$Active metabolites of spironolactone have $t_{1/2}$ of >15 hours.

$^d$Active metabolites accumulate in CKD. Adapted from Karin (82).
the kidney, and that albumin administration might enhance natriuresis. This conjecture was supported in an early proof-of-concept study (20), but subsequent larger studies have produced mixed results. A relatively recent meta-analysis concluded that the existing data, albeit of poor quality, suggest transient effects of modest clinical significance for coadministration of albumin with furosemide in hypoalbuminemic patients (21). A similar assessment is reflected in the Kidney Disease Improving Global Outcomes guidelines for diuretic treatment of GN (22). Nevertheless, most recent studies have enrolled patients whose serum albumin concentrations exceeded 2 g/dl, so that these considerations may not apply for severely hypoalbuminemic patients. Some guidelines continue to suggest that albumin infusion should be used as an adjunct to diuretics when nephrotic patients appear to have vascular volume depletion (or appear to be “underfilled”) (23).

Approximately 50% of an administered furosemide dose is excreted unchanged into the urine. The remainder appears to be eliminated by glucuronidation, predominantly also in the kidney. Torsemide and bumetanide are eliminated both by hepatic processes and urinary excretion, although hepatic metabolism may predominate, especially for torsemide (24). The differences in metabolic fate mean that the \( t_{1/2} \) of furosemide is prolonged in kidney failure, where both excretion by the kidney and kidney-mediated glucuronidation are slowed. In contrast, the \( t_{1/2} \) of torsemide and bumetanide tend to be preserved in CKD (25). Although the ratio of equipotent doses of furosemide-to-bumetanide is 40:1 in normal individuals, that ratio declines as kidney function progresses (26). Although this apparent increase in furosemide potency may seem beneficial, it also likely increases the toxic potential of furosemide in the setting of AKI. Deafness and tinnitus from loop diuretics appear to result primarily from high serum concentrations, which inhibit an Na-K-2Cl isoform (NKCC1, encoded by \( SLC12A2 \)). This transport protein, which is different from that expressed along the thick ascending limb, is expressed by the stria vascularis and participates in secretion of potassium-rich endolymph (27,28). This complication was seen more frequently in the past when very large bolus doses of loop diuretics were used to forestall dialysis (29).

In one meta-analysis of furosemide use for patients with AKI, the odds ratio for hearing loss was more than three when high-dose furosemide was used; it should be noted, however, that the doses cited in that analysis (1–3 g daily) exceed those currently recommended (30). The tendency of bolus infusion to lead to high peak furosemide concentrations is one reason that many investigators recommend continuous infusions instead (1).

Loop diuretics exert their actions by binding to transport proteins along the luminal membrane of thick ascending limb cells. To gain access to the tubular fluid and therefore to their sites of activity, they must be secreted across the proximal tubule, as their protein binding in plasma largely prevents glomerular filtration. Although some data suggest that bumetanide is also delivered into the tubule lumen by filtration (31), a preponderance of evidence suggests that it also gains entry primarily via secretion (32). Peritubular uptake is mediated by the organic anion transporters OAT1 and OAT3, whereas the apically located multidrug resistance-associated protein 4 (Mrp-4) appears to mediate at least a portion of secretion into the tubular fluid. Mice lacking OAT1, OAT3, or Mrp-4 are resistant to loop and thiazide diuretics, illustrating the functional importance of these proteins (31,33).

Although human mutations in OAT1 have not been described, these pathways may be inhibited by drugs and endogenous toxins, thereby causing diuretic resistance (31). Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit diuretic secretion and alter diuretic responsiveness, and because of their frequent use, are an important cause of heart failure exacerbations (34). Yet other classes of drugs, including antihyper tensives, antibiotics, and antivirals, may also interact with these transporters and cause resistance (35). Endogenous metabolites also compete for diuretic secretion, including indoxyl sulfate, carboxymethyl-propyl-furanpropionate, p-cresol sulfate, and kynurestate, which accumulate in CKD (36). In all of these situations, the natriuretic dose-response curve is shifted to the right (Figure 3A).

There are additional reasons that CKD is a loop diuretic-resistant state. Metabolic acidosis, which is frequently observed in uremia, depolarizes the membrane potential of proximal tubule cells (37), which also decreases organic anion secretion, an effect that may explain why diuretic secretion is enhanced by alkalosis (38). In addition to a shift in the dose-response curve, patients with CKD and those taking NSAIDs have a downward shift of the ceiling natriuresis, when expressed as absolute sodium excretion (rather than fractional). The mechanism for resistance attributable to NSAIDs is complex. Loop diuretic inhibition of NaCl reabsorption at the macula densa stimulates both renin secretion and prostaglandin (PG) production, the latter predominantly via cyclooxygenase-2 (39). When this happens, PG E2 feeds back on tubules, contributing to the resulting natriuresis by inhibiting NaCl transport along the thick ascending limb and collecting duct (40,41). NSAIDs block this PG-mediated antinatriuresis. When used chronically, NSAIDs increase the abundance and activity of NKCC2 along the thick ascending limb (42). Additionally, loop diuretics inhibit the second transporter isoform, NKCC1, mentioned above, which is also expressed by vascular smooth muscle cells; loop diuretics contribute to afferent arteriolar vasodilation by blocking this transporter (43), thus helping to maintain GFR despite a lower ECF volume. Again, this compensatory adaptation is largely dependent on PG production and can be blocked by NSAIDs. The clinical consequence of these effects is evident in the association between recent use of NSAIDs and risk for hospitalization in patients with heart failure (34). In fact, the combination of three classes of drugs that affect hemodynamics of the kidney, loop diuretics, angiotensin-converting inhibitors (or receptor blockers), and NSAIDs, is associated with AKI (44).

CKD also impairs the natriuretic response to diuretics through a different mechanism. It is frequently noted that the maximal natriuretic capacity of loop diuretics is maintained in the face of CKD, when natriuresis is measured as a fraction of filtered load (Figure 3A). Yet the maximal natriuretic effect of these diuretics, when measured as the more clinically relevant absolute rate, is markedly reduced (Figure 3B). This is because, as GFR and filtered sodium load decrease, kidneys suppress sodium...
reabsorption by the tubule to maintain the balance between dietary salt intake and urinary salt excretion. This suppression occurs along the thick ascending limb, so that even when a diuretic reaches the segment and inhibits the transporter, its net effect is reduced. Thus, NSAIDs and CKD cause diuretic resistance both by shifting the diuretic dose-response curve to the right (which can be overcome by higher doses) and by reducing maximal natriuresis (which cannot; compare Figure 3, A and B). This phenomenon likely explains the reduced effectiveness of distal convoluted tubule diuretics in CKD. If, like loop diuretics, maximal fractional sodium excretion remains constant as GFR declines, then their already modest ceiling will appear minimal when GFR is low (Figure 3C).

Loop diuretics are characterized by relatively short $t_{1/2}$ (see Table 2). Thus, the initial natriuresis typically wanes within 3–6 hours, so that a single daily dose leaves some 16–21 hours for the kidneys to compensate for salt and water losses. For individuals in steady state, the phenomenon of “postdiuretic NaCl retention” defines that fact that urinary NaCl excretion declines below the baseline when the diuretic effect wears off. This is typically true until another dose of diuretic is administered (45). It should be noted, however, that although this relationship applies to patients who are at steady state (and thereby excreting their daily intake of salt), it is altered in patients with decompensated edema, who may present during a period of positive NaCl balance, with urinary [NaCl] very low, even without diuretic administration. In this case, any increase in urinary NaCl excretion will be beneficial.

Regardless of these differences, the net NaCl loss from a diuretic typically results from a short period of natriuresis and a longer period of antinatriuresis. This accounts for the usual recommendation to use loop diuretics twice daily; clearly, from inspection of the $t_{1/2}$, this imperative is most important when using bumetanide and least so with torsemide. As noted above, when CKD progresses, the $t_{1/2}$ of furosemide is prolonged, increasing its apparent relative potency versus bumetanide. Even when administered twice daily, however, long internatriuretic periods limit drug efficacy; this is most important when dietary NaCl intake is high, as NaCl retention by the kidneys will lead to more positive NaCl balance.

One strategy to address $t_{1/2}$ issues, at least for hospitalized patients, is to infuse loop diuretics continuously. Although the advantages of this approach over high-dose bolus treatment remain largely speculative (46), the physiologic basis for this approach is appealing, and recent stepped care guidelines (see below) recommend continuous infusions (47). Along these lines, an investigational extended release formulation of torsemide that delivers torsemide to the circulation over 8–12 hours was reported recently to double salt and water losses in normal volunteers after a single dose, without increasing potassium excretion (48). If such a formulation, which should avoid some of the obvious pharmacokinetic limitations of short acting loop diuretics, works as well in patients with heart failure or nephrotic syndrome, it may change the standard approach to treatment.

Somewhat different considerations apply to patients with cirrhotic ascites. Here, relative gastrointestinal absorption tends to be preserved (49). Coupled with the tendency for relative underfilling in this setting, it is typically recommended to avoid intravenous diuretics, if possible (50). In this situation, a combination of furosemide with spironolactone, in a ratio of 40 mg furosemide to 100 mg spironolactone, is recommended in most patients, to balance efficacy and safety, although in patients with concomitant kidney disease, this ratio may need to be adjusted, with the goal of maintaining normokalemia (51).

**Using Diuretics Effectively to Treat ECF Volume Expansion**

When diuretics are initiated to treat edema, whether in a patient with normal or abnormal kidney function, it is essential to confirm that the dose provides a tubule concentration that exceeds the threshold (Figure 1B). That this threshold has been reached can be detected by monitoring electrolyte and weight changes. A discrepancy between diuresis and weight loss in outpatients
suggests that excessive NaCl consumption is limiting effectiveness; in this case, measuring 24-hour urine sodium excretion, using creatinine to confirm collection adequacy, may confirm excessive NaCl intake, although single urine [Na+] collections may not give fully accurate results (52). For hospitalized patients, a dose reaching the threshold should lead to an increase in urine volume during the 6 hours that follow a dose. On the basis of the relationship of plasma diuretic concentration and time shown in Figure 2B, diuresis should occur more promptly after an intravenous dose. This difference may be especially pronounced if furosemide is the diuretic chosen. If an effect is not observed during this period, it is customary to double the dose, for example from 20 to 40 mg of furosemide or from 80 to 160 mg of furosemide, a recommendation predicated on the dose-response curve shown in Figure 2C. The dose is then escalated to a maximal safe level, as discussed below. Although loop diuretics are typically administered twice daily, there is no reason to introduce a second daily dose if the first dose does not exceed the threshold. Once a threshold has been reached, however, most patients will require two daily doses.

Although dose recommendations for loop diuretics have been published, on the basis of pharmacokinetic and pharmacodynamic considerations (24) or expert consensus (53), several more specific dose ranges have been tested in clinical trials. For acute decompensated heart failure, Felker and colleagues compared doses 2.5-times the home daily dose with one-times the home daily dose, given intravenously. Although differences in the primary outcome were not observed using the higher dose in this trial, prespecified secondary outcomes were encouraging, and negative consequences were not observed. Importantly, this and other recent trials, including those for patients with cardiorenal syndrome, aimed for 3–5 L of diuresis per day for initial treatment (47), rates that are more aggressive than often targeted. These studies emphasize that, for hospitalized patients, an aggressive approach to diuresis is often safe as well as effective. Prior concerns that diuretic drugs might be harmful to the kidney or the system overall, therefore, likely reflected confounding by indication when determined in observational trials (54). In fact, post hoc analyses of large trials suggest that those who experience a moderate increase in creatinine (worsening kidney function) may actually have better prognosis than those who do not (55,56).

The net or therapeutic natriuretic response to a diuretic is determined by the difference between the net sodium excreted in the urine and the sodium consumed. Although increasing a diuretic dose above the ceiling does not increase the maximal minute-natriuresis (the maximal rate of NaCl excretion per given time, see Figure 2C), it often increases the net natriuresis by prolonging the period during which the diuretic concentration exceeds the threshold (see Figure 2A). This is one reason that current guidelines for heart failure may recommend doses that exceed ceiling doses and are multiples of prior or home doses (see below and Ellison and Felker [45]).

In both normal individuals and in patients with ECF volume expansion, there is a linear relationship between ECF volume and sodium excretion (U$_{NaV}$), elegantly elucidated by Walser (57). This is similar to, but distinct from, the pressure natriuresis, which describes the relationship between mean arterial pressure and U$_{NaV}$. Diuretics are recommended universally to treat symptomatic ECF volume expansion, with rare exceptions, and therapeutic success is considered to be reduction in ECF. This invariably requires initial sodium and water losses, induced by diuretic doses that exceed the threshold (Figure 4). Yet the situation changes as initial treatment moves toward successful chronic treatment. At any therapeutically active dose, natriuresis wanes as ECF declines, an effect often called the “braking phenomenon” (58). This means that, at steady state, the individual returns to NaCl balance, during which urinary NaCl excretion is equal to dietary NaCl intake once again. This occurs, however, at a lower ECF volume than before treatment. Functionally, then, chronic diuretic treatment shifts the relationship between ECF volume and U$_{NaV}$ to the left (see Figure 4), thereby permitting NaCl excretion rates to again equal intake, albeit with lower ECF volume. It should be noted, however, that although daily NaCl excretion normalizes, the pattern of salt and water loss remains more episodic, so that a patient may complain that the diuretic regimen is increasing urine output.

Although the braking phenomenon is adaptive once ECF volume has been reduced successfully, it is maladaptive, when it occurs in the setting of persistent ECF volume expansion. Many factors resulting primarily from changes in ECF volume, such as stimulation of nerves innervating the kidney and activation of the renin-angiotensin system, likely contribute to braking (59,60), but it is now recognized that adaptive changes in segments other than the thick ascending limb also play an important role (61,62). Remodeling of the distal nephron occurs (63), leading to hypertrophy and hyperplasia, especially of distal segments. This results from increased salt delivery (64), increased angiotensin II (65) and aldosterone concentrations (66), and changes in potassium balance. The consequences of remodeling are that distal tubules increase their transport capacity to rival that of thick ascending limbs; for this reason, more of the NaCl that escapes the loop of Henle is reabsorbed distally, and net natriuresis is reduced.

Figure 4. | Relationship between ECF volume and sodium excretion, based on (57). Diuretics shift this curve upward (blue line), but may make it shallower. The baseline sodium excretion rate (which equals intake) is shown by the dashed line. After a diuretic is started, urinary sodium excretion rises by shifting to a new curve (from point 1 to point 2). Gradually (through the braking phenomenon) urinary sodium excretion declines back to the baseline level, but at a new and reduced ECF volume (from point 2 to point 3).
Adding a thiazide or thiazide-like drug will help to treat, and may even prevent, this type of adaptation and restore diuretic efficacy. Most commonly, especially in patients with CKD, metolazone is chosen as the second agent, although other thiazides may be equally effective (67). Interestingly, at least three factors may contribute to these beneficial effects. First, by blocking transport along the distal tubule, a site exhibiting transport activation, the potency of these normally weak diuretics will be increased (68). Second, when oral metolazone or chlorothalidone is used in this situation, its longer t_{1/2} (approximately 14 and 50 hours [69]) means that postdiuretic NaCl retention may be attenuated. Third, these drugs may mitigate distal nephron remodeling and activation of the thiazide-sensitive NCC (70). Nevertheless, a key hazard of this approach is the substantial potential for hypokalemia (71). As hypokalemia is now recognized as the dominant factor activating NCC (72), such secondary effects counteract the goal of adding a second class of diuretic. In this situation, lower or less frequent doses may gain the benefits as well as limit the risks.

Evidence-Based Diuretic Dosing for ECF Volume Expansion

Although recommendations for loop diuretic dosing have traditionally been made on the basis of pharmacological properties, some more recent studies of acute decompensated heart failure have focused on patient-centered outcomes. The Diuretic Strategies in Patients with Acute Decompensated Heart Failure trial compared high and low doses of loop diuretics for acute decompensated heart failure and showed that the higher dose (2.5 times the home daily dose) is well tolerated and effective. One concern about aggressive diuretic approaches in this situation is worsening kidney function, which was used as a harm signal in this study. Yet worsening kidney function in this trial, as indicated by a rise in creatinine, is actually associated with better, rather than worse, prognosis (55). When adequate diuresis does not occur, a stepped care approach, shown in Table 3, has been recommended (47). Although not compared directly with other approaches, this algorithm was used successfully in randomized trials and proved at least as effective as invasive techniques, such as ultrafiltration (73).

More limited but compelling data suggest that patients with cirrhotic ascites are best treated with a combination of furosemide and spironolactone, at a ratio of 40:100 mg (74). This preserves the plasma potassium concentration in most patients, although it may need to be adjusted if abnormalities occur. For patients with nephrotic syndrome, diuretic binding was previously suggested to contribute to resistance. Yet a study comparing the natriuretic effect of loop diuretics with and without protein displacement indicated clearly that this factor was not contributing (75). Another contributor in this situation is the cleavage of the epithelial sodium channel by filtered proteases (76); recent animal data suggest that this may be a target for intervention, with either protease inhibitors or amiloride (77).

Diuretics for AKI

Recommendations for and against diuretic use in AKI have varied widely. At the end of the 20th century, extremely high diuretic doses were often used, which can convert oliguric to nonoliguric AKI, but were found to be associated with deafness and no change in mortality in controlled trials (78). A later retrospective trial suggested that diuretic use in patients with AKI is associated with increased mortality, and suggested that “the widespread use of diuretics in critically ill patients with acute renal failure should be discouraged” (79). Yet, statistical approaches cannot overcome the inherent limitations in such retrospective studies. To address this concern and reduce confounding by indication, Grams et al. performed a post hoc analysis of data for patients with AKI from the Fluid and Catheter Treatment Trial (80). In this trial, patients with adult respiratory distress syndrome were randomized to liberal or restrictive fluid policies; for those randomized to restricted fluid, diuretics were used aggressively. The results of this trial suggested that patients who developed AKI who were randomized to a strategy that involved more diuretic administration had a lower adjusted odds ratio for death (80). Although even this trial is not definitive, it suggested that prior reported adverse outcomes from diuretic use in AKI likely did reflect confounding by indication. At this point, it seems reasonable to use diuretics as an adjunct in AKI to maintain euvoolemia. It is generally best, however, to avoid very high doses, and avoid using diuretics to delay more definitive treatments, such as dialysis.

Summary

Diuretic drugs, agents that target solute transport along the nephron, are used commonly in individuals with normal or reduced kidney function. Each diuretic drug has a unique pharmacokinetic profile, but such differences may not receive sufficient consideration when the drugs are used therapeutically. Recent large, clinical trials now provide an evidence base for diuretic treatment of heart failure. Yet, even when such evidence is available, a deep understanding of diuretic pharmacokinetics and pharmacodynamics enhances the clinical approach to diuresis. As the drugs have substantial ability to ameliorate breathlessness and edema, the goal of optimizing their use should improve patient-focused clinical outcomes. The development of diuretic drugs has been one of

<table>
<thead>
<tr>
<th>Level</th>
<th>Current Daily Furosemide Dose,g</th>
<th>Bolus</th>
<th>Infusion Rate, mg/h</th>
<th>Metolazone (Oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤80 mg</td>
<td>40</td>
<td>5</td>
<td>0 mg daily</td>
</tr>
<tr>
<td>2</td>
<td>81–160 mg</td>
<td>80</td>
<td>10</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>3</td>
<td>161–240 mg</td>
<td>80</td>
<td>20</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>4</td>
<td>≥240 mg</td>
<td>80</td>
<td>30</td>
<td>5 mg twice daily</td>
</tr>
</tbody>
</table>

*Diuretic equivalents: 40 mg furosemide is considered equivalent to 1 mg bumetanide/20 mg torsemide. Adapted from Grodin et al. (47) and Bart et al. (73). The full algorithm provided in the references includes additional considerations for vasodilator, inotropic, or mechanical therapy for patients who fail to respond within 48 h.
the greatest accomplishments of scientific medicine; the persistence of disorders of ECF volume into the 21st century means that these drugs will continue to play central roles in medical practice for the foreseeable future.

Disclosures
Dr. Ellison has nothing to disclose.

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Correction
Ellison DH: Clinical Pharmacology in Diuretic Use. 
*Clin J Am Soc Nephrol* 14: 1248–1257, 2019; DOI:
https://doi.org/10.2215/CJN.09630818.

Because of author error, the following corrections have been issued for this article:

1. The label for “Absorption Varies” in Figure 2A should have referenced Table 2, not Table 1. The corrected Figure 2 is reprinted below.

2. The authors have also reported the following typographical error on page 1251: “antinatriuresis” should have been “natriuresis.” The corrected word is in boldface font *in situ* in the paragraph below from the article.

   “There are additional reasons that CKD is a loop diuretic–resistant state. Metabolic acidosis, which is frequently observed in uremia, depolarizes the membrane potential of proximal tubule cells (37), which also decreases organic anion secretion, an effect that may explain why diuretic secretion is enhanced by alkalosis (38). In addition to a shift in the dose-response curve, patients with CKD and those taking NSAIDs have a downward shift of
the ceiling natriuresis, when expressed as absolute sodium excretion (rather than fractional). The mechanism for resistance attributable to NSAIDs is complex. Loop diuretic inhibition of NaCl reabsorption at the macula densa stimulates both renin secretion and prostaglandin (PG) production, the latter predominantly via cyclooxygenase-2 (39). When this happens, PG E2 feeds back on tubules, contributing to the resulting natriuresis by inhibiting NaCl transport along the thick ascending limb and collecting duct (40,41). NSAIDs block this PG-mediated natriuresis. When used chronically, NSAIDs increase the abundance and activity of NKCC2 along the thick ascending limb (42). Additionally, loop diuretics inhibit the second transporter isoform, NKCC1, mentioned above, which is also expressed by vascular smooth muscle cells; loop diuretics contribute to afferent arteriolar vasodilation by blocking this transporter (43), thus helping to maintain GFR despite a lower ECF volume. Again, this compensatory adaptation is largely dependent on PG production and can be blocked by NSAIDs. The clinical consequence of these effects is evident in the association between recent use of NSAIDs and risk for hospitalization in patients with heart failure (34). In fact, the combination of three classes of drugs that affect hemodynamics of the kidney, loop diuretics, angiotensin-converting inhibitors (or receptor blockers), and NSAIDs, is associated with AKI (44)."