Diuretics are commonly prescribed to manage various conditions in the general population. They can continue to play a role in dialysis patients to manage extracellular fluid volume and hypertension and to reduce the tendency to hyperkalemia. Nevertheless, diuretics are often stopped when patients commence dialysis. Several studies have shown that preserved residual renal function in dialysis patients is associated with improved patient survival. Although the association between diuretic use and preserved residual renal function is still controversial, the numerous clinical benefits offered by diuretics render those agents valuable in dialysis patients with urine output.

Loop diuretics are generally the agents of choice in end-stage renal disease. They need to be used at higher doses because of pharmacokinetic changes in the context of diminishing renal clearance. Other classes of diuretics can still be used in end-stage renal disease, but usually in conjunction with loop diuretics or for benefits independent of diuresis. Complications can occur with the use of diuretics, but are avoidable with appropriate use. Dose-related ototoxicity, especially with concomitant use of other ototoxic medications, can occur. Hyperkalemia is possible with the use of potassium-sparing diuretics, but studies suggest that these agents can be safely administered with close monitoring.

Key words
Diuretics, hemodialysis, pharmacology, adverse events, residual kidney function

Introduction
Diuretics are commonly prescribed in the general population to manage various conditions such as hypertension, edema, and congestive heart failure (1). Although dialysis patients have similar conditions, the use of diuretics declines sharply in these individuals after they have been on dialysis for 2 years. Furthermore, the prescribing practices of clinicians appear to vary dramatically across dialysis facilities, with 0% – 83.9% of dialysis patients being on diuretics (2). Some studies have shown an association between diuretic use and better preserved residual renal function (RRF) in dialysis patients (2), but that finding is still controversial.

In this review, we explore the mechanism of action of diuretics and their utility in patients with a diminished glomerular filtration rate (GFR), and we revisit the importance of RRF. We also discuss the clinical benefits and risks of diuretics, specifically in the peritoneal dialysis (PD) and hemodialysis (HD) populations.

Discussion

Mechanism of action of diuretics
Loop diuretics block the Na⁺-K⁺-2Cl⁻ co-transporter. They inhibit sodium and chloride reabsorption in the thick ascending limb of the loop of Henle and cause increased secretion of water, potassium, sodium, and chloride. Furosemide, bumetanide, and ethacrynic acid are examples of this class of diuretics.

Loop diuretics are the drug of choice in patients with end-stage renal disease (ESRD) because they are thought to be effective to some degree at low GFR (3). However, a reduction in GFR results in less tubular transport of the diuretic to the lumen of the nephron (the site of action), which limits the maximum achievable diuretic effect. In fact, in patients with a GFR below 15 mL/min, secretion of the loop diuretic into tubular fluid is only 10% – 20% of that seen in individuals with normal renal function (4). To overcome that difference, a sufficiently high dose (that is, 160 – 200 mg intravenous furosemide) might be needed to attain effective diuresis or maximal natriuresis (approaching 20% of the filtered Na⁺ load) (4,5). In patients with a GFR below 10 mL/min and a daily urine volume below 100 mL, the effect of diuretics might be minimal (6).
Thiazide diuretics block the Na⁺-Cl co-transporter in the distal tubule. Hydrochlorothiazide, metolazone, indapamide, and chlorothalidone belong to this class of diuretics. As in the case of loop diuretics, decreased delivery of thiazide diuretics to the nephron lumen requires that sufficiently high doses be given in the context of diminishing GFR. Using hydrochlorothiazide as an example, 50 – 100 mg daily might have to be prescribed in mild-to-moderate renal failure and 100 – 200 mg daily in severe renal failure (5). Still, even at those high doses, hydrochlorothiazide, because of its low potency and limited natriuresis, is not typically effective in severe renal failure (4). To achieve effective diuresis with a thiazide diuretic in patients with a GFR below 30 mL/min, the more common approach is to give it in combination with a loop diuretic (7,8). The combination generates additive natriuresis in the setting of loop diuretic resistance and can allow for lower doses of the latter drug to be administered. Metolazone has a long half-life and is compartmentalized in red blood cells. For those reasons, it can maintain diuresis over a considerable period of time, rendering it the thiazide of choice as an adjunct to a loop diuretic in ESRD (4). Finally, because thiazide diuretics lower peripheral vascular resistance independent of natriuresis, some clinicians use them for their antihypertensive effects in ESRD, although that use is not routinely recommended (9).

Potassium-sparing diuretics act in the distal renal tubule. Spironolactone, amiloride, and triamterene are examples of this drug class. Spironolactone competes with aldosterone for receptor sites and increases sodium, chloride, and water excretion while conserving potassium. Amiloride and triamterene block epithelial sodium channels that inhibit sodium reabsorption, decrease the function of the Na–K pump, and lead to potassium retention. True to their name, they can cause hyperkalemia (especially in patients with diabetes) and should be used with caution (7).

Other less commonly used classes of diuretics are osmotic diuretics (mannitol) and carbonic anhydrase inhibitors (acetazolamide).

Importance of RRF

The 2006 clinical practice guidelines for PD adequacy from the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative emphasize the importance of monitoring and preserving residual kidney function (10). Similarly, the clinical practice guidelines for HD adequacy state that “one should strive to preserve residual kidney function in HD patients” (11). Both guidelines are supplemented with good evidence and are presented as grade A recommendations. They are supported by the reanalysis of the CANUSA PD study, which showed that, for each additional 250 mL of urine excreted per day, the relative risk for death declined by 36% (12). In the HD population, the CHOICE study showed that RRF (defined as 250 mL of urine output daily) was associated with better survival and quality of life, less inflammation, and a significantly lower erythropoietin requirement (13).

Unfortunately, longitudinal studies have shown that RRF declines progressively with time on dialysis (6), and therefore any intervention that can potentially slow RRF decline in dialysis patients is considered advantageous.

Clinical benefits of diuretics in dialysis patients

It had been postulated that loop diuretics might potentially play a role in slowing the observed decline in RRF. Medcalf et al. showed that patients newly started on continuous ambulatory PD, with RRF at baseline, maintained their urine volume over 1 year when given an oral daily dose of 250 mg furosemide (6). At the 12-month mark, a significant mean difference of 340 mL in daily urine volume was observed that was associated with a significant difference in sodium excretion (which the authors postulated to be the mechanism behind the greater urine volume). In the HD population, observational studies have suggested the same outcome (14). It is important to note that Medcalf et al. showed that, although furosemide increased urine volume, it had no effect on preserving or slowing the decline in small-solute clearance (6).

The Dialysis Outcomes and Practice Patterns Study postulated that the association between lower mortality and diuretic use observed in their analysis is one more example of the known survival benefit conferred by RRF (2); however, there are other potential explanations. One confounding explanation for the finding is that RRF might itself be associated with lower mortality and that patient selection bias might be operating (in that diuretics are usually prescribed to patients who have RRF). However, there are mechanisms whereby diuretics might plausibly affect patient survival.
ELECTROLYTE BALANCE AND VOLUME CONTROL

The advantage conferred by preserved RRF might be related to the urine volume excreted and maintenance of euvoletic status (12). Based on the mechanism of action of loop diuretics, the beneficial effects observed in dialysis patients could be explained by the removal of sodium and water. That removal plays a crucial role in preventing volume overload and its sequelae (such as left ventricular hypertrophy, congestive heart failure, and uncontrolled hypertension). Further, RRF allows for increased clearance of middle molecules, reduced blood pressure, improved hemoglobin status and phosphorus control, reduced left ventricular hypertrophy, and fewer comorbid conditions—all potentially leading to improved patient survival (15).

In HD patients, it is possible that diuretic use helps to preserve RRF and to improve survival by reducing interdialytic fluid accumulation and thus minimizing hypotensive episodes during dialysis, which have been associated with greater morbidity and mortality (2). Hyperkalemia has also been less often observed in patients on diuretics (2).

IMPACT ON QUALITY OF LIFE AND NUTRITION

Patients on dialysis oftentimes have diets that restrict sodium, potassium, phosphorus, and fluid intake. Diuretic use might allow patients to liberalize their diet and fluid intake, which could potentially be more palatable for them and might increase compliance with other therapies. In PD patients specifically, the use of diuretics might perhaps allow for less frequent and less hypertonic dextrose exchanges, which could be convenient for the patient and could theoretically diminish systemic glucose loading and perhaps protect the peritoneal membrane from damaging high glucose concentrations. As well, PD patients with higher RRF have been observed to have a lower risk of peritonitis (15).

Side effects and complications of diuretics

ALDOSTERONE ANTAGONISTS AND HYPERKALEMIA

Dialysis patients have an increased extracellular fluid volume and high aldosterone levels, which can contribute to cardiovascular risk. The potassium-sparing diuretics spironolactone and eplerenone are also known as aldosterone antagonists. They can improve cardiac function and reduce left ventricular mass in moderate-to-severe heart failure in dialysis patients (15). However, these patients might also be at particularly high risk for developing hyperkalemia while on aldosterone antagonists; rates are reported to be as high as 10%, particularly at higher doses (16). The risk is theoretically intensified with the concomitant use of medications such as angiotensin-convertase enzyme inhibitors, angiotensin II receptor blockers, trimethoprim, antifungals, and nonsteroidal anti-inflammatory drugs, which can also cause hyperkalemia (4,5,17).

Baker et al. reviewed the literature on the safe use of mineralocorticoid antagonists in patients with ESRD undergoing HD and suggested that those agents could be safely used in HD patients because the incidence of severe hyperkalemia remained low (16). It is noteworthy, though, that most studies lacked a true control arm and had small patient populations and relatively short follow-up periods. The doses used in the reviewed studies varied from spironolactone 12.5 mg 3 times weekly to 300 mg daily. Taheri et al. performed a prospective randomized double-blind placebo-controlled clinical trial evaluating the safety and efficacy of spironolactone 25 mg every other day in 18 continuous ambulatory PD patients with New York Heart Association class III or IV heart failure (18). Those authors showed that potassium levels rose in both groups, with no statistically significant difference, and only 1 patient in the treatment group developed hyperkalemia (defined as >5.7 mmol/L potassium). It is noteworthy that patients on angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were not excluded from the studies. In general, aldosterone antagonists can be used in ESRD patients for several cardiac benefits (although those benefits have not been extrapolated to the dialysis population), but K+ levels should be monitored frequently, especially with concomitant use of other medications that could exacerbate hyperkalemia.

LOOP DIURETICS AND OTOTOXICITY

Loop diuretics can cause ototoxicity, usually in patients receiving high intravenous doses while taking other other ototoxic medications, particularly aminoglycoside antibiotics (5). The ototoxicity is usually transient and reversible. Limited data suggest that the frequency of ototoxicity seems to be higher with furosemide than with bumetanide and even higher with ethacrynic acid (4). For that reason, ethacrynic...
acid is reserved mainly for patients with an allergy to furosemide (5). Several older studies have explored furosemide ototoxicity, one of which found that, among patients with severe renal failure, infusion of furosemide at a constant rate of 25 mg/min caused noticeable hearing loss in two thirds of patients. When given at a rate of 15 mg/min, only minor hearing loss was reported. The authors concluded that furosemide should be given at a rate of less than 4 mg/min to avoid hearing loss (19). Rastogi et al. found no hearing loss among renal patients receiving daily oral doses of furosemide up to 2 g (20), although Rifkin et al. and Gallagher et al. reported permanent hearing loss from smaller oral doses (21,22).

Although ESRD patients require higher doses of furosemide to attain adequate diuretic effect, it is important to note that a “ceiling effect” has been observed in loop diuretics for a dose at which the fractional percentage of sodium excretion (the diuretic effect) plateaus for any incremental increase in the dose. Continuing to increase the dose of a diuretic therefore results in no additional diuretic effect, but theoretically exposes the patient to more side effects. The usual maximum intravenous dose of furosemide is 80 – 160 mg in moderate renal insufficiency and 160 – 200 mg in severe renal insufficiency (the equivalent oral dose is double) (5).

**Summary**

Diuretics are often underutilized in dialysis patients or even stopped once patients are initiated on dialysis. Several studies have suggested that, in ESRD patients who continue to have RRF, many benefits accrue from continuation of diuretics. Loop diuretics are the drugs of choice, and they might need to be used at higher doses to attain optimal diuresis. Some side effects can occur, but those effects can be avoided and managed with close patient monitoring.

**Disclosures**

The authors have no financial conflicts of interest to disclose.

**References**


Corresponding author: Joanne M. Bargman, MD, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario M5G 2C4 Canada.

E-mail: joanne.bargman@uhn.ca