Management of Hyperkalemia in Dialysis Patients

Nirupama Putcha and Michael Allon
Division of Nephrology, University of Alabama at Birmingham, Birmingham, Alabama

ABSTRACT

Hyperkalemia is common in patients with end-stage renal disease, and may result in serious electrocardiographic abnormalities. Dialysis is the definitive treatment of hyperkalemia in these patients. Intravenous calcium is used to stabilize the myocardium. Intravenous insulin and nebulized albuterol lower serum potassium acutely, by shifting it into the cells. Despite their widespread use, neither intravenous bicarbonate nor cation exchange resins are effective in lowering serum potassium acutely. Prevention of hyperkalemia currently rests largely upon dietary compliance and avoidance of medications that may promote hyperkalemia. Prolonged fasting may provoke hyperkalemia, which can be prevented by administration of intravenous dextrose.

Hyperkalemia is common in patients with end-stage renal disease. Due to its effect on cardiac conductivity, hyperkalemia is a subject of great concern among clinicians. This review will discuss current views of its mechanisms in dialysis patients, treatment modalities, and approaches to its prevention.

Potassium Homeostasis

The total potassium content of an average 70 kg person is approximately 3500 mmol. Of this, 98% is contained inside the cells, while only 2% is in the extracellular compartment. Due to this asymmetric distribution, small shifts between the intracellular and extracellular fluid compartments may result in major changes in serum-potassium concentration. The average American diet contains about 100 mmol of potassium, an amount exceeding the total intracellular content (1). Maintenance of serum potassium in the normal range therefore depends on both excretion of potassium out of the body, as well as potassium shifts between the extracellular and intracellular compartments (2,3).

Potassium excretion depends primarily on renal, and to a lesser extent on intestinal excretion. In individuals with normal renal function, 90–95% of an oral potassium load is excreted in the urine, while the rest is excreted in the stool. An increase in dietary potassium intake results in an adaptive increase in urinary and gastrointestinal potassium excretion. Complete excretion of an oral potassium load is a relatively slow process, requiring 6–12 hours to be completed. Dietary potassium is initially absorbed into the extracellular fluid compartment, a process that would acutely result in hyperkalemia, were it not for the rapid shifts of potassium from the extracellular to the intracellular fluid compartments (accomplished within minutes) that defend against this complication. The major factors stimulating potassium shifts from the extracellular to the intracellular fluid compartments (extrarenal potassium disposal) include insulin, catecholamines, and metabolic alkalosis.

Given that the kidneys are largely responsible for potassium excretion, it is not surprising that patients with end-stage renal disease are at a high risk for developing hyperkalemia. In this patient population, extrarenal potassium disposal is paramount in defending against hyperkalemia. Increased levels of aldosterone enhance intestinal secretion of potassium in dialysis patients by stimulating the ouabain-sensitive sodium-potassium pump on intestinal epithelium. Notwithstanding this adaptation, life-threatening hyperkalemia is a frequent menace in patients with end-stage renal disease (ESRD; 1–6).

Hyperkalemia—Definitions, Incidence, and Symptoms

Hyperkalemia is the condition of overabundance of potassium in the extracellular compartment (7). It is defined as a serum-potassium concentration ≥5.5 mm (1). Although hyperkalemia may occur in the outpatient setting, it is more commonly observed in hospitalized patients, at a frequency ranging between 1% and 10% (7). Among hemodialysis patients, the mortality due to hyperkalemia has been estimated at 3.1 per 1000 patient-years (8). In any given month, 5–10% of hemodialysis patients have hyperkalemia. Furthermore, 24% of patients with ESRD require emergency hemodialysis at some time for treatment of hyperkalemia (9).

Common causes of hyperkalemia in dialysis patients include excess intake of potassium, most often through

Address correspondence to: Michael Allon, MD, Division of Nephrology, PB, Room 226, 1530 Third Avenue South, Birmingham, AL 35294, or e-mail: mdallon@uab.edu.

Seminars in Dialysis—Vol 20, No 5 (September–October) 2007 pp. 431–439
DOI: 10.1111/j.1525-139X.2007.00312.x

dietary indiscretion but occasionally from overzealous intravenous or oral supplementation. In addition, inadequate dialytic potassium removal may be a cause of hyperkalemia in patients with end-stage renal disease who skip dialysis treatments or cut their sessions short. Potassium shifts from the intracellular to the extracellular compartments may also contribute to hyperkalemia. Such shifts can be attributed to postdialytic rebound, drugs (including nonselective beta-blockers, digitalis, and succinylcholine), insulin deficiency, metabolic acidosis, and rhabdomyolysis. Drugs that impair urinary potassium excretion (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers, nonsteriodal anti-inflammatory drugs, trimethoprim, and heparin) may aggravate hyperkalemia in dialysis patients with residual kidney function. Finally, a defect in cellular sodium-potassium ATPase has been demonstrated in patients with ESRD leading to decreased potassium uptake into cells (1).

In cells with excitability such as muscle and cardiac tissues, hyperkalemia leads to hyperpolarization of cells, making them less able to depolarize when necessary (1). The effect of hyperkalemia upon cardiac conductivity is its most feared clinical consequence. Electrocardiographic findings depend upon the level of hyperkalemia. "Mild" hyperkalemia (serum potassium 5.5–6.5 mm), is often associated with "peaked" T-waves. "Moderate" hyperkalemia (serum potassium 6.5–8.0 mm) is also associated with a prolonged PR interval (time in seconds from the start of the P-wave to the beginning of the Q-wave in an EKG) flattened P-waves, and QRS complex (the combination of Q-, R-, and S-waves in an EKG, signifying ventricular depolarization) widening. Finally, "severe" hyperkalemia (>8 mm) is usually associated with a total absence of P-waves; intraventricular, fascicular, and bundle branch blocks; and most ominously with a "sine-wave" and asystole (10).

As a general rule, greater degrees of hyperkalemia are associated with more severe EKG abnormalities. Thus, 46–64% of patients with a serum potassium >6.0 mm exhibit at least one EKG abnormality (11). However, the association is far from perfect. Thus, there have been case reports of patients with severe hyperkalemia (>9.0 mm) with completely normal EKGs (12). Moreover, two studies performed in chronic hemodialysis patients have reported a poor correlation between EKG changes and the magnitude of hyperkalemia. Aslam et al. (13) reported no correlation between the T-wave amplitude or the T-wave to R-wave amplitude ratio and serum-potassium concentrations. The clinical significance of their observations was limited by potassium concentrations within the normal range in most of their study subjects. Of greater clinical relevance was the study by Ngugi et al. (14), which included patients with a wider range of serum-potassium levels including overtly hyperkalemic values (5.0–7.9 mm). EKG abnormalities were observed in all (31/31) patients with a serum potassium ≥6 mm, but also in 23% (9/39) of those with values between 5.0–5.9 mm. Among the subset with EKG abnormalities on presentation, the EKG normalized 30 minutes after initiating treatment in 50% (20/40) of patients.

Less commonly, severe hyperkalemia may profoundly affect skeletal muscle, manifesting as motor weakness and parasthesias. In severe cases, the patient may present with flaccid paralysis that resolves completely once the hyperkalemia has been treated. Interestingly, muscle weakness due to hyperkalemia rarely affects the diaphragm, cranial nerves, or sensory function (3).

Treatment of Hyperkalemia

Stabilization of the Myocardium

Immediate therapy of hyperkalemia (see Table 1) is directed at preventing its life-threatening consequences on cardiac conductivity. Rapid intravenous infusion of calcium salts (either calcium gluconate or calcium chloride) reliably improves hyperkalemic EKG changes within minutes. By increasing serum-calcium concentrations, this intervention increases the threshold for the cardiac muscle action potential, thereby decreasing excitability (9). Five medical textbooks (two nephrology, two internal medicine, and one emergency medicine) advocate calcium gluconate in all hyperkalemic patients with EKG changes (2,9,15–17). In addition, two of these references advocate calcium administration in patients whose serum potassium is >6.0–6.5 mm, even in the absence of EKG changes (9,15).

Transcellular Shifts

Hemodialysis is the definitive therapy for severe hyperkalemia with EKG changes in patients with end-stage renal disease. Because initiation of hemodialysis frequently requires 1–2 hours, it is important to institute temporizing measures to lower serum potassium acutely. These therapies stimulate rapid potassium shifts from the extracellular to the intracellular fluid compartments. The principal treatment modalities in this category include insulin, beta-2 adrenergic agonists, and bicarbonate. The next section will summarize the evidence evaluating each of these therapies for acute hyperkalemia in dialysis patients.

Insulin Three studies have demonstrated the utility of intravenous insulin (in combination with glucose) for the rapid correction of hyperkalemia in patients with ESRD. The first study observed a significant drop in plasma potassium in 10 patients given insulin (5 mU/kg/minute) in combination with glucose

TABLE 1. Treatment of hyperkalemia

Stabilize myocardium with calcium salts (calcium gluconate 10 ml as an i.v. bolus)
Shift potassium into cells:
Intravenous dextrose (50 ml of 50% i.v. bolus) + regular insulin (10 units i.v. bolus)
AND
10–20 mg nebulized albuterol over 10 minutes (2–4 ml of 5 mg/ml albuterol solution) (72)
OR
Subcutaneous terbutaline injection (7 μg/kg subcutaneously)
Potassium removal with dialysis

(5 mg/kg/minute) as a constant infusion. Despite the concurrent administration of dextrose, half of the patients developed hypoglycemia. This study also found that intravenous insulin with dextrose was more efficacious than bicarbonate or epinephrine in treating hyperkalemia acutely (18). The second study found that 10 units of intravenous regular insulin followed by 50 ml of a 50% glucose solution (both given as an intravenous bolus) significantly decreased serum potassium within 15 minutes, but also produced hypoglycemia in 75% of patients within 1 hour (19). The third study found that insulin was the most rapid and efficacious single-drug therapy for hyperkalemia in acute and chronic renal failure. In this study 10 units of regular insulin and 50 ml of 50% dextrose were given as an intravenous bolus. A decrease in serum-glucose levels was observed in all patients, but only 20% developed frank hypoglycemia (14). In summary, insulin is the most reliable drug therapy for acute treatment of hyperkalemia in ESRD patients. However, hypoglycemia is a common side effect of this therapy, despite the coadministration of dextrose. In concordance with this idea, another group suggested that perhaps glucose infusion preceding insulin administration would prevent this potentially serious complication (20). Muto et al. (21) evaluated the efficacy of dextrose alone (in the absence of insulin infusion) for treatment of hyperkalemia in patients with ESRD, as well as in healthy controls. The authors' rationale was that exogenous glucose, by stimulating endogenous secretion of insulin, would raise plasma insulin levels sufficiently to increase transcellular shifts of potassium. The authors observed a potassium-lowering effect of glucose infusion in ESRD patients, but not in healthy controls. This treatment modality may correct hyperkalemia in dialysis patients without exposing them to the risk of hypoglycemia. However, it may not be effective in diabetic dialysis patients, particularly those with insulin-dependent diabetes or those in whom endogenous insulin production is deficient. In fact, administration of dextrose alone in such patients may result in a paradoxical increase in serum potassium, by producing plasma hypertonicity that promotes potassium shift out of the cells (solvent drag) (2). Coadministration of intravenous insulin helps to attenuate this increase. In summary, intravenous insulin with glucose remains the first-line therapy for acute treatment of severe hyperkalemia in dialysis patients. The treating nephrologist should anticipate the occurrence of hypoglycemia in patients receiving this treatment.

Albuterol Montoliu et al. (22) first reported that intravenous albuterol (0.5 mg) acutely lowered serum potassium in stable dialysis patients with mild hyperkalemia (mean serum potassium 5.6 mm) by about 1.1 mm within 30 minutes. Moreover, in patients with severe hyperkalemia (mean serum potassium 7 mm) this therapy lowered the serum potassium to a mean of 5.6 mm within 30 minutes. Because albuterol produced a rise in serum insulin, it was unclear whether the potassium-lowering effect of albuterol was mediated directly by its beta-2 adrenergic stimulation or indirectly by its effect on insulin. However, in a subgroup of patients with insulin-deficient diabetes, albuterol produced similar decreases in serum potassium despite negligible changes in free C peptide levels, supporting a direct action of the drug. Ngugi et al. (14) reported a similar decrease in serum potassium following administration of 0.5 mg of intravenous albuterol. A subgroup of ESRD patients treated with intravenous albuterol experienced tremor (17 out of 44) or generalized discomfort (10 out of 44). Furthermore, the patients' heart rate increased from a mean of 77–99 bpm within 30 minutes of albuterol administration, but returned to baseline within 3 hours (22). The intravenous formulation of albuterol is not available in the United States. However, nebulized albuterol is also effective for the treatment of hyperkalemia in ESRD patients. In one study,10 mg of nebulized albuterol lowered serum potassium by a mean of 0.62 mm, and 20 mg reduced serum potassium by 0.98 mm after 2 hours (23). In another study, 15 mg of nebulized albuterol lowered the serum potassium by a mean of 0.9 mm (24). Allon et al. (23) observed increases in heart rate after nebulized albuterol, although the magnitude of increase (from 87 to 94 bpm after 20 mg of nebulized albuterol) was smaller than that reported after administration of intravenous albuterol. Furthermore, among the patients given nebulized albuterol, Montoliu et al. (24) found that only four out of 10 experienced a mild tremor while only one of 10 patients in the Allon et al. (23) study experienced anxiety.

In summary, both intravenous and nebulized albuterol are efficacious in acutely decreasing the serum potassium in ESRD patients, but nebulized albuterol is less likely than the intravenous drug to produce tachycardia and symptoms. In contrast, a study comparing intravenous to nebulized albuterol in 11 children with ESRD found a greater decrement in plasma potassium with intravenous therapy, but a more sustained effect (up to 5 hours) with nebulized therapy. The two routes of administration resulted in similar side-effect profiles, including mild tremor, vasomotor flushing, and a modest increase in heart rate (25).

The dose of nebulized albuterol reported to decrease serum potassium in ESRD patients (10–20 mg) is several-fold higher than that used as a bronchodilator in patients with asthma or chronic obstructive lung disease (2.5–5 mg). It is important to emphasize that the lungs are simply being used as the route to introduce albuterol into the systemic circulation. It appears that the systemic absorption is quite low, as 10–20 mg of nebulized albuterol produce a comparable potassium-lowering dose to that achieved with 0.5 mg intravenous albuterol. Lower doses of nebulized albuterol are ineffective in lowering serum potassium in ESRD patients. Thus, for example, 1.2 mg of albuterol administered by metered dose inhaler (MDI) produced a very modest decrease in serum potassium (from a baseline of approximately 5.5 to around 5.3 mm, 5.2 mm, and just below 5.1 mm at 5, 30, and 60 minutes, respectively), despite a comparable increase in heart rate (26). Albuterol solutions for nebulized administration are packaged at two concentrations: 0.83 mg/ml and 5 mg/ml). Administering 20 mg of nebulized albuterol requires using 4 ml of the concentrated

drug, as compared with 24 ml of the dilute formulation. For this reason, the concentrated formulation should be specified in the physician's order.

Beta-2 adrenergic agonists may also be effective in the treatment of hyperkalemia when administered subcutaneously. In a recent study, subcutaneous terbutaline (7 μg/kg) was administered to 14 chronic hemodialysis patients and produced a mean 1.3 mm decrease in serum potassium. Changes in heart rate were similar to those found in previous studies using intravenous and nebulized albuterol, with a mean increase of 26 bpm, but a wide inter-subject variation (27). This study established subcutaneous terbutaline as an alternate approach to nebulized albuterol, that is remarkable for its speed and simplicity of administration, as well as its rapid onset.

The combination of albuterol and insulin has been evaluated for treating hyperkalemia in ESRD patients. One study observed comparable potassium-lowering effects with intravenous albuterol and insulin with glucose. Combined administration of both drugs resulted in a significantly greater potassium-lowering effect, as compared with each drug alone (28). Likewise, a second study observed a similar potassium-lowering effect in ESRD patients treated with nebulized albuterol (10 mg) alone or insulin with glucose. Combining both therapies resulted in a greater decrease in serum potassium, as compared with each therapy alone (19). In both studies the frequency of hypoglycemia observed in patients given insulin with glucose was markedly attenuated by the coadministration of albuterol (19,28).

In summary, albuterol is effective for the rapid treatment of hyperkalemia in ESRD patients. The nebulized form is easier to use than the intravenous form, and may produce fewer side effects. Finally, coadministration of albuterol and insulin with glucose has an additive potassium-lowering effect, while reducing the likelihood of hypoglycemia seen after insulin with glucose administered alone.

Epinephrine Epinephrine at physiologic doses has been shown to decrease serum potassium in healthy controls. In contrast, epinephrine at low doses produces a paradoxical increase in plasma potassium in ESRD patients (29). Even high doses of epinephrine result in only a modest decrease in serum potassium in dialysis patients. Moreover, the response is unpredictable, with only 50% of patients showing a significant effect (18).

Epinephrine is a mixed alpha- and beta-adrenergic receptor. Whereas beta-2 stimulation shifts potassium into the cells, alpha-adrenergic stimulation shifts potassium out of the cells. Thus, the net effect of epinephrine on serum potassium in a given individual reflects the relative balance of beta-2 and alpha-adrenergic stimulation. The resistance of dialysis patients to the potassium-lowering effect of epinephrine may reflect either a greater alpha component or a blunted beta component, as compared with healthy controls. The first explanation seems more likely, as administration of epinephrine in patients with concurrent beta-blockade (i.e., "pure" alpha-adrenergic stimulation) results in significantly greater increases in serum potassium in ESRD patients, as compared with those observed in healthy controls (4). For this reason, the use of pure beta-2 agonists is the preferred modality for acute treatment of hyperkalemia in ESRD patients.

Bicarbonate Bicarbonate infusion has long been recommended for the acute treatment of hyperkalemia in dialysis patients. A survey of nephrology training program directors in 1989 showed that after calcium gluconate, bicarbonate was the most trusted therapy for acute hyperkalemia in the oliguric patient (30). An early study by Fraley and Adler showed that infusion of 88–132 mmol of bicarbonate in one liter of 5% dextrose caused significant drops in serum potassium in hyperkalemic patients (not all necessarily chronic dialysis patients) (31).

Despite the widely held belief in the efficacy of bicarbonate in treating hyperkalemia in dialysis patients, a number of studies have cast doubt on its utility. Blumberg et al. administered either isotonic or hypertonic bicarbonate (without glucose) to hemodialysis patients. Neither therapy elicited a sizeable decrement in serum potassium. In fact, both therapies resulted in an increase in serum potassium at 60 minutes (18). In a subsequent investigation, the same group evaluated the effect of sodium bicarbonate infusion over several hours. The earliest significant decrease in serum potassium occurred at 4 hours, and it was very modest, from a baseline of 5.44–5.3 mm. In fact, the slight decline in serum potassium could be explained purely on the basis of extracellular fluid volume expansion and dilution of extracellular potassium (32). In another study hypertonic bicarbonate infusions decreased serum potassium at 10 minutes, but increased serum potassium at 180 minutes. In contrast, isotonic bicarbonate decreased serum potassium at 180 minutes. The authors attributed the increase in serum potassium with hypertonic bicarbonate to an increase in plasma osmolality, which in turn, promoted potassium shift out of the cells (33). The beneficial effect of bicarbonate administration on hyperkalemia in the study by Fraley and Adler (31) may have been due in part to the coadministration of glucose, which would itself lower serum potassium by stimulating endogenous insulin secretion. Furthermore, Fraley and Adler (31) included in their study chronic kidney disease patients not yet on dialysis. In this subpopulation, bicarbonate administration may lower serum potassium by stimulating urinary potassium excretion.

In summary, the published studies demonstrate that administration of bicarbonate to ESRD patients is ineffective in treating hyperkalemia within a useful time frame (approximately 2 hours, or until dialysis can be instituted), and thus should no longer be considered as adequate therapy.

Although bicarbonate alone is not useful for the acute treatment of hyperkalemia in ESRD patients, there is some debate about its ability to potentiate the potassium-lowering effects of insulin or albuterol. In one study conducted by Kim (34), the combination of bicarbonate and insulin with glucose was more effective in decreasing serum potassium in dialysis patients than insulin and glucose alone. In contrast, a second study in dialysis patients performed by Allon and Shanklin (35) found that the combination did not enhance the effect of

insulin and glucose alone. The study done by Kim (34) enrolled hyperkalemic patients (average pretreatment serum potassium of 6.2–6.4 mm), whereas Allon and Shanklin (35) studied normokalemic patients (serum potassium 4.23–4.34 mm). The study conducted by Allon and Shanklin (35) was placebo-controlled, whereas the one by Kim (34) was open-labeled. The two studies also differed in the amount and type of bicarbonate administered. Kim's (34) study administered hypertonic sodium bicarbonate (2 mmol/minute over 1 hour), whereas Allon and Shanklin's (35) study administered isotonic bicarbonate (1.5 mmol/minute over 1 hour).

Potassium Removal

Although the above interventions are critical for the acute treatment of hyperkalemia in ESRD patients, definitive therapy entails removal of potassium, either through the gastrointestinal (GI) tract or through dialysis.

Cation Exchange Resins For many decades, cation exchange resins in conjunction with cathartics (e.g., Kayexalate + sorbitol) have been used routinely in the acute therapy of hyperkalemia in dialysis patients. While early studies found that chronic administration (1 week) of Kayexalate decreased serum-potassium concentration, they did not evaluate the acute use of this agent (36,37). It was not until 1998 that one-time use of resin-cathartic therapy for potassium removal was studied independently of other treatment modalities. This study looked at dialysis patients over a 12-hour period of time after being given one of the five different regimens including placebo, resin only, phenolphthalein-docusate, phenolphthalein-docusate + resin, and sorbitol + resin. Over 12 hours, serum potassium of patients in all five groups failed to decrease compared with pretreatment values. Although the study enrolled primarily normokalemic (serum potassium 3.4–5.7 mm) patients, there was no correlation between pretreatment serum potassium and stool potassium output or the magnitude of change in serum potassium (36,38). Thus, although chronic administration of resins may be useful in preventing hyperkalemia in ESRD patients, the administration of resins with or without cathartics in the acute setting is of limited benefit due to its slow onset of action (minimum of 2 hours) (39) and limited potassium-lowering effect.

Not only is resin-cathartic therapy of doubtful benefit in the acute management of hyperkalemia among dialysis patients, it may also produce potentially life-threatening complications. After several case reports implicated Kayexalate + sorbitol enemas in causing colonic necrosis and occasionally perforation in ESRD patients, one group tested this hypothesis in uremic rats. This group found that enemas containing sorbitol or Kayexalate + sorbitol produced transmural necrosis in uremic rats, whereas enemas containing either Kayexalate alone or normal saline enemas had no such complications (40). Enemas containing Kayexalate alone (without sorbitol) may be safer, especially because sorbitol serves no useful purpose in the enema formulation (41). The occurrence of gastric and ileocecal ulcers has been reported in a single patient after oral administration of Kayexalate in sorbitol. Combining Kayexalate with another cathartic may be beneficial to patients (41).

Dialysis Dialysis is the definitive treatment for severe hyperkalemia in ESRD patients. Several parameters of dialysis may affect the magnitude of potassium removal, including dialysate concentrations of potassium, bicarbonate and glucose, as well as dialyzer blood flow.

Most of the potassium removal occurs during the first 2 hours of dialysis, when the potassium gradient between the blood and dialysate is highest. Hemodialysis is most commonly performed using a 2-mm dialysate potassium concentration (2-K). Lowering the dialysate potassium concentration should enhance potassium removal by increasing the potassium gradient between the blood and the dialysate. Hou et al. (42) compared the effect of three different dialysate potassium concentrations on potassium removal: 2 mm (2-K), 1 mm (1-K), and 0 mm (0-K) in 11 chronic hemodialysis patients. The total amount of potassium removed in a dialysis session averaged 51 mmol with the 2-K dialysate, 63 mmol with the 1-K dialysate, and 78 mmol with the 0-K dialysate. There was a greater decrease in serum potassium with 1-K dialysate, as compared with a 2-K dialysate, but no further decrease if one switched to a 0-K bath. Dolson et al. (43) compared the effect of dialysis sessions using 1-K, 2-K, and 3-K dialysate. The lower the dialysate potassium concentration, the greater the amount of potassium removed, and the lower the final postdialysis serum potassium. Similarly, Zehnder et al. (44) compared three dialysate potassium concentrations (0-K, 1-K, and 2-K), and observed greater total potassium removal with lower dialysate potassium concentrations.

Although lowering the dialysate potassium concentration is a simple measure to increase potassium removal, it may impair dialysis adequacy. Thus, Dolson and Adrogue (45) observed a lower efficiency of dialysis (URR and Kt/V) with 1-K versus 3-K dialysate. They postulated that the hypokalemia associated with the use of low potassium dialysate results in vasodilation, which in turn impairs blood flow to skeletal muscle, thereby reducing urea clearance. In contrast, Zehnder et al. (44) found no difference in urea clearance between 0-K, 1-K, and 2-K dialysates. The discrepancy in findings between these two studies may be attributable to differences in the dialysate glucose and bicarbonate concentrations used.

Use of a low potassium dialysate may also expose patients to potential cardiac side effects. Morrison et al. (46) showed that a 2-K dialysate could provoke complex ventricular arrhythmias during dialysis in some patients, which usually resolved once the dialysate potassium concentration was increased to 3.5 mm. Hou et al. (42) used Holter monitoring during a 4-hour dialysis session and for 6 hours postdialysis in 11 patients dialyzed with 0-K, 1-K, and 2-K dialysates. Most patients had only isolated premature ventricular complexes or atrial premature contractions whose frequency did not correlate with the dialysate potassium concentrations. However, one patient had significant ventricular ectopy during dialysis

with all three potassium baths, that was most severe with the 0-K bath, and least severe with the 3-K bath. Furthermore, when this patient was dialyzed with a 3-K bath, the ventricular ectopy seen during the other dialysis sessions was significantly improved.

In summary, low-potassium dialysate enhances potassium removal, and may be more efficient for treatment of acute hyperkalemia in patients with ESRD. However, it may potentially reduce the efficiency of urea clearance. In susceptible patients, it may also aggravate ventricular arrhythmias.

The dialysate bicarbonate concentration may also impact the magnitude of potassium decrement during dialysis. In a randomized, double-blind, three-sequence, crossover study, Heguilen et al. (47) compared changes in serum potassium, potassium removal, and potassium rebound in patients treated with three different dialysate bicarbonate concentrations (27, 35, and 39 mm). While serum potassium decreased more rapidly with the high bicarbonate dialysis (39 mm), the total potassium removal was not significantly different between the therapies. They postulated that the higher bicarbonate concentration favored an intracellular potassium shift, explaining these differences. Their observations suggest that in patients with profound hyperkalemia the use of high bicarbonate dialysate may be used to accelerate the decrease in serum potassium. However, the safety of this method should be further studied.

Another study by Capdevila et al. (48) compared the efficiency of potassium removal in bicarbonate versus acetate hemodialysis. Because a rise in serum bicarbonate may shift potassium into cells during hemodialysis, the authors postulated that bicarbonate dialysis reduced potassium removal and increased potassium rebound postdialysis. They actually found that potassium removal was comparable with both dialysates although potassium did rebound more with the bicarbonate buffer. The authors concluded that bicarbonate-induced intracellular shifts of potassium occur late in the course of hemodialysis and therefore has little effect on total potassium removal (which occured mainly in the first 2 hours of treatment).

Sherman et al. (49) evaluated the effect of dialysate glucose concentrations upon dialytic potassium removal. They compared the magnitude of potassium removal between glucose-free dialysate and dialysate containing 200 mg/dl of glucose. One might expect that the decreased endogenous insulin from the glucose-free dialysate would allow a greater amount of potassium to stay in the extracellular compartment for dialytic removal, hence allowing for greater amounts of potassium removal from glucose free dialysate. Although potassium removal tended to be higher with glucose-free dialysate, the difference did not achieve statistical significance, probably due to the limited number of patients studied. Ward et al. (50) did observe a significantly higher potassium removal with glucose-free dialysate, as compared with glucose-containing dialysate.

Dialysis blood flow may also influence potassium removal. Thus, one study found that higher blood flows resulted in significantly greater decreases in serum-potassium concentration and potassium removal. Presumably, increasing the dialysis blood flow enhances potassium clearance by maximizing the potassium gradient between the blood and the dialysate (51).

Finally, acute treatment of hyperkalemia with insulin or albuterol, by promoting potassium shifts from the extracellular to the intracellular fluid compartment, may attenuate potassium removal during the subsequent dialysis session. Allon and Shanklin (52) showed that administration of nebulized albuterol 30 minutes prior to dialysis significantly lowered the potassium removal during dialysis. Once the beta-adrenergic effect wears off (after 4–6 hours), there may be an exaggerated rebound in serum potassium. Although not tested in this study, it is likely that a similar phenomenon might be observed in patients receiving intravenous insulin with dextrose prior to their dialysis session. This study enrolled normokalemic patients, so it is not clear whether similar observations would be obtained in hyperkalemic dialysis patients.

Prevention

Dietary Restriction

Prevention of hyperkalemia (see Table 2) is of utmost importance in dialysis patients. Given that the kidneys are the major route for excretion of dietary potassium, limiting potassium intake is critical in functionally anephric dialysis patients. Hemodialysis patients should restrict their daily dietary potassium to 2–3 g or to 8–17 mg/kg (53). This entails restricting their intake of high-potassium foods, such as oranges, melons, nuts, several varieties of squash, beans, lentils, potatoes, chocolate, and salt substitutes. A resource developed by the National Kidney Foundation outlines helpful ways to reduce potassium content in potassium-rich foods, with methods such as "leaching" (54). Renal dietitians play a critical role in educating patients about dietary potassium restriction.

Fasting Hyperkalemia

The contribution of dietary potassium intake to hyperkalemia in ESRD patients is intuitively obvious. What is less frequently appreciated is the propensity of dialysis patients to develop hyperkalemia during prolonged fasting (>8 hours). This phenomenon may be observed when patients are fasted in preparation for sur-

TABLE 2. Prevention of hyperkalemia

Restriction of dietary potassium to 8–17 mg/kg/day
Administration of 10% dextrose at 50 ml/minute during prolonged fasting (add 10 units of regular insulin per liter if diabetic)
Avoidance of medications that may increase serum potassium, including potassium sparing diuretics[a], angiotensin converting enzyme inhibitors[a], heparin, nonsteroidal anti-inflammatory drugs, and nonselective beta-blockers
Potential therapies needing further study
Mineralocorticoids, such as fludrocortisone
Bisacodyl
Fosinopril
Low dialysate sodium concentration

[a]Historically these medications are avoided; however, recent study calls this practice into question. See text.

gery or diagnostic studies, or if they are unable to eat due to gastroparesis. It is not unusual for a dialysis patient's surgery to be canceled when hyperkalemia is noted in the preoperative laboratory test.

Fasting hyperkalemia is a consequence of suppressed endogenous insulin secretion. The decreased levels of plasma insulin result in a net shift of potassium from the cells into the extracellular fluid compartment. Unlike healthy controls, who can easily excrete the excess extracellular potassium in the urine, dialysis patients lacking this adaptive mechanism develop hyperkalemia. As a result, prolonged fasting produces a progressive increase of serum potassium in dialysis patients, but no change in normal controls (55). Deranged epinephrine metabolism in ESRD patients may further aggravate fasting hyperkalemia (29). Whenever prolonged fasting becomes necessary in dialysis patients, close monitoring for hyperkalemia is recommended. Fasting hyperkalemia can be easily prevented in nondiabetic dialysis patients by administering 10% dextrose at 50 ml/hour for the duration of their fast. The exogenous glucose, by stimulating endogenous insulin secretion, prevents potassium shifts out of the cell. In diabetic dialysis patients, who have impaired endogenous insulin secretion, one should add regular insulin (10 U/l) to the dextrose infusion (29).

Medications

Patients who are relatively new to dialysis usually have residual kidney function and some capacity for urinary potassium excretion. Drugs that impair renal potassium excretion may predispose such patients to hyperkalemia. These drugs include potassium-sparing diuretics, ACE inhibitors, angiotensin-receptor blockers, heparin, and nonsteroidal anti-inflammatory drugs. In addition, drugs that impair extrarenal potassium disposal may promote hyperkalemia in both new and established (anuric) dialysis patients. In addition, oral contraceptives containing drospirenone (e.g., Yasmin) may also produce hyperkalemia.

Given that beta-2 adrenergic stimulation fuels potassium uptake into cells, it is not surprising that nonselective (i.e., beta-1 + beta-2) beta-blockers can exacerbate hyperkalemia after physical exercise (56), or during fasting, a finding which is absent when patients are given selective beta-1 blockers (57). Therefore, when beta-blockers are clinically indicated in ESRD patients, beta-1 selective blockers, such as metoprolol or atenolol, should be prescribed preferentially (58). Atenolol in particular has been shown to be not only safe, but also effective when administered thrice weekly (after dialysis) for blood pressure control without causing significant hyperkalemia (59). Carvedilol, a nonselective beta-blocker used commonly for treatment of heart failure, may induce hyperkalemia in dialysis patients.

ACE inhibitors may induce hyperkalemia in dialysis patients with residual kidney function. However, this class of drugs may be of great therapeutic value in dialysis patients, due to their high risk of cardiovascular complications. The Heart Outcomes and Prevention Evaluation (HOPE) trial observed a higher incidence of cardiovascular death, myocardial infarction, and stroke in patients with chronic kidney disease, as compared with patients with normal renal function (60). Two recent studies have shown that ACE inhibitors are effective therapy for improving cardiovascular outcomes in dialysis patients. The HOPE trial reported that ramipril significantly reduced the frequency of cardiovascular death, myocardial infarction, and stroke in patients with chronic kidney disease (60). A retrospective study of hemodialysis patients between 1994 and 2000 found that those patients receiving at least 6 months of therapy with ACE inhibitors had significantly reduced all-cause mortality, which was attributed to a reduction in cardiovascular death (61).

Unfortunately, neither study assessed the effects ACE inhibitors on serum potassium in their study populations. A study by Knoll et al. (62) found that hemodialysis patients taking ACE inhibitors or angiotensin receptor blockers were twice as likely to develop hyperkalemia, as compared with patients not receiving these therapies. Therefore, it is recommended that when ACE inhibitors or angiotensin receptor blockers are prescribed to hemodialysis patients, serum potassium should be monitored weekly during the first month, and then monthly (58).

Potassium-sparing diuretics, such as spironolactone and eplerenone, may also result in hyperkalemia. However, just as with ACE inhibitors, spironolactone reduces cardiovascular mortality in patients with congestive heart failure (63). Two studies evaluated the safety of short-term spironolactone therapy in hemodialysis patients. The first study administered 2 weeks of thrice-weekly therapy with 12.5 mg spironolactone, followed by 2 weeks of thrice-weekly therapy with 25 mg spironolactone. A thrice-weekly dose was chosen, as this dose was considered equivalent to daily dosing in patients with normal renal function. There was no significant increase in plasma potassium during the course of therapy, as compared with the baseline value (64). A second study evaluated 4 weeks of spironolactone 25 mg daily, and observed a nonsignificant increase in serum potassium, from 4.6 to 4.9 mm. However, four patients had single potassium levels between 5.5 and 6.0 mm and one developed frank hyperkalemia (7.6 mm) (65).

The strict enrollment criteria in both studies likely excluded those patients at highest risk of developing hyperkalemia. The true risk of hyperkalemia with spironolactone therapy would likely be higher if the drug were prescribed more liberally in a nonresearch setting. Moreover, both studies evaluated only short-term (< 1 month) administration of aldosterone. An ongoing clinical trial is evaluating the effect of chronic (6 months) spironolactone on serum potassium in hemodialysis patients (NCT00328809, www.clinicaltrials.gov).

Therapeutic Options for Prevention

The most widely studied therapeutic modality for long-term prevention of inter-dialytic hyperkalemia is the mineralocorticoid fludrocortisone. Theoretically, mineralocorticoids should lower serum potassium by two mechanisms: (1) augmentation of colonic potassium excretion, and (2) stimulation of sodium-potassium

ATPase on the cell membrane to enhance extrarenal potassium disposal (66). Singhal et al. (66) treated 21 chronic dialysis patients with fludrocortisone, 0.1–0.3 mg daily, for several months. The mean predialysis potassium concentration decreased significantly from 5.6 to 4.9 mm. A second study by Furuya et al. (67) evaluated gradually increasing doses of fludrocortisone (maximum 0.2 mg daily) over 4 months. The maximum decrease in serum potassium was observed during the third month (with 0.15 mg fludrocortisone daily), with a decrease from 5.57 to 4.89 mm.

In contrast to these promising results, a recent, randomized-controlled trial conducted by Kaisar et al. (68) observed an insignificant difference in predialysis serum potassium between dialysis patients receiving fludrocortisone, 0.1 mg daily, compared with those patients in the control group (4.8 versus 5.2 mm). The lack of potassium-lowering effect in this last study may have been due to prescription of a lower dose of mineralocorticoid, as compared with the maximum dose administered in the two previous studies (66,67). Furthermore, although this was the only randomized-controlled trial evaluating the effect of chronic mineralocorticoids on serum potassium in hemodialysis patients, it was not placebo controlled, nor was there any mention of blinding. Furthermore, although cointervention bias was a possible explanation for the favorable results of the Furuya (67) study, Singhal et al. (66) did not discontinue any medications that would possibly affect serum-potassium levels [consistent with the Kaisar (68) study] yet still found a significant decrement in serum potassium with mineralocorticoid therapy. A definitive, randomized, double-blinded, clinical trial is needed to settle this important clinical question.

Another possible modality for the reduction of interdialytic potassium is the daily administration of the laxative, bisacodyl. In one study, hemodialysis patients were given variable daily doses (5–10 mg daily) to induce an acceptable level of stool frequency, and serum potassium was measured 2–3 times weekly for 2 weeks. The investigators observed a significant decrease in the mean predialysis serum potassium during bisacodyl therapy (from 5.9 to 5.5 mm during treatment), a change that was not found in healthy controls. Although stool frequency increased, frank diarrhea was not reported. Importantly, the patients showed no signs of hypovolemia, and no significant changes in blood pressure (systolic and diastolic) or weight. The authors postulated that bisacodyl stimulates production of cAMP, which in turn activates potassium secretion in the gut (possibly mediated by apical potassium channels in the gut epithelium) (69). Thus, bisacodyl is a promising and safe therapy for the chronic management of hyperkalemia in ESRD, and merits further investigation.

Another potential therapy for preventing hyperkalemia in dialysis patients is the chronic use of the ACE inhibitor, fosinopril. At first glance, the use of this agent appears counter-intuitive, given the aforementioned propensity of ACE inhibitors to induce hyperkalemia. However, unlike other ACE inhibitors, fosinopril is excreted by two pathways, renal as well as biliary. Surprisingly, the authors found a statistically significant drop in average predialysis potassium levels from 6.7 to 5.5 mm after 4 weeks of drug therapy. The predialysis serum potassium decreased in 20 of 23 patients treated with fosinopril, and subsequently increased after the drug was discontinued (70). It is possible that fosinopril enhances potassium secretion through the biliary system, thereby decreasing the interdialytic serum-potassium levels. Unfortunately, this study did not compare the effect of fosinopril to that of a different ACE inhibitor.

Finally, lowering the dialysate sodium concentration may be helpful in prevention of hyperkalemia in hemodialysis patients. In a randomized, single-blind crossover trial, reducing the dialysate sodium concentration from 145 to 137 mm (in two different dialysis sessions approximately 2 weeks apart) blunted the postdialysis rebound rise in serum potassium, even though dialytic potassium removal was comparable in both groups. Serum-potassium concentrations at 2, 24, 48, and 68 hours postdialysis were significantly lower in patients treated with low sodium dialysate, as compared with the standard sodium dialysate (4.2 versus 4.7, 4.9 versus 5.7, 5.5 versus 6.3, and 5.7 versus 6.5 mm at 2, 24, 48, and 68 hours postdialysis, respectively). The authors postulated low sodium dialysate reduced postdialysis plasma osmolality and decreased solvent drag, thereby attenuating potassium shifts out of the cells (71). These results suggest that a low sodium dialysate has much promise for the prevention of interdialytic hyperkalemia.

In conclusion, hyperkalemia is a significant problem among patients with end-stage renal disease. Various therapeutic options exist for the immediate treatment of the condition, including insulin with glucose, albuterol, and more recently subcutaneous terbutaline. Ultimately, if levels of hyperkalemia are significant enough, potassium removal is indicated. The utility of cation-exchange resins has not been demonstrated despite its widespread use; dialytic removal of potassium remains the mainstay of therapy. Many options have been proposed for the prevention of interdialytic hyperkalemia. However, further work is needed to sort out the utility of these therapies. Prevention currently rests largely upon compliance with diet and a thoughtful use of medication regimens.

References

1. Jamison RL: Hyperkalemia in the patient with end-stage renal disease. *Nephrology Rounds* 4:1–6, 2001
2. Allon M: Disorders of potassium metabolism. In: Greenburg A (ed). *Primer on Kidney Diseases*, 2nd edn. San Diego, CA: National Kidney Foundation, 1998:98–106
3. Ahmed J, Weisberg L: Hyperkalemia in dialysis patients. *Semin Dial* 14:348–356, 2001
4. Allon M: Treatment and prevention of hyperkalemia in end-stage renal disease. *Kidney Int* 43:1197–1209, 1993
5. Allon M: Hyperkalemia in end-stage renal disease: mechanisms and management. *J Am Soc Nephrol* 6:1134–1142, 1995
6. Kamel K, Wei C: Controversial issues in the treatment of hyperkalaemia. *Nephrol Dial Transplant* 18:2215–2218, 2003
7. Mahoney BA, Smith WAD, Lo DS, Tsoi K, Tonelli M, Clase CM: Emergency interventions for hyperkalaemia (Review). *Cochrane Database of Syst Rev* 2005, 2: CD003235
8. U.S. Renal Data System: Annual Data Report, Reference Tables. Available at http://www.usrds.org/reference.htm, accessed November 30, 2006
9. Mount DB, Zandi-Nejad K: Hyperkalemia. In: Brenner BM (ed). *The Kidney*, 7th edn. Philadelphia, PA: Saunders, 2004:1017–1025
10. Mattu A, Brady W, Robinson D: Electrocardiographic manifestations of hyperkalemia. *Am J Emerg Med* 18:721–729, 2000

11. Evans K, Reddan D, Szczech L: Nondialytic management of hyperkalemia and pulmonary edema among end-stage renal disease patients: an evaluation of the evidence. *Semin Dial* 17:22–29, 2004
12. Szerlip HM, Weiss J, Singer I: Profound hyperkalemia without electrocardiographic manifestations. *Am J Kidney Dis* 7:461–465, 1986
13. Aslam S, Friedman E, Ifudu O: Electrocardiography is unreliable in detecting potentially lethal hyperkalemia in haemodialysis patients. *Nephrol Dial Transplant* 17:1639–1642, 2002
14. Ngugi N, McLigeyo S, Kayima J: Treatment of hyperkalaemia by altering the transcellular gradient in patients with renal failure: effect of various therapeutic approaches. *East Afr Med J* 73:503–509, 1997
15. Crews D, Chi P, Choi M: Disorders of potassium homeostasis. In: Piccini JP, Nilsson KR (ed). *The Osler Medical Handbook*, 2nd edn. Baltimore: The Johns Hopkins University, 2006:800–804
16. Kokko JP: Hyperkalemia and potassium excess. In: Goldman L, Ausiello D (ed). *Cecil Textbook of Medicine*, 22nd edn. Philadelphia: W.B. Saunders and Company, 2004:686–687
17. Gibbs M, Tayal V: Electrolyte disturbances. In: Marx JA (ed). *Rosen's Emergency Medicine: Concepts and Clinical Practice*, 6th edn. Philadelphia: Mosby, 2006:1939–1941
18. Blumberg A, Weidmann P, Shaw S, Gnadinger M: Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med* 85:507–512, 1988
19. Allon M, Copkney C: Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int* 38:869–872, 1990
20. Ljutic D, Rumboldt Z: Should glucose be administered before, with or after insulin, in the management of hyperkalemia? *Ren Fail* 15:73–76, 1993
21. Muto S, Sebata K, Watanabe H, Shoji F, et al.: Effect of oral glucose administration on serum potassium concentration in hemodialysis patients. *Am J Kidney Dis* 46:697–705, 2005
22. Montoliu J, Lens S, Revert L: Potassium-lowering effect of albuterol for hyperkalemia in renal failure. *Arch Intern Med* 147:713–717, 1987
23. Allon M, Dunlay R, Copkney C: Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 110:426–429, 1989
24. Montoliu J, Almirall J, Ponz E, Campistol JM, et al.: Treatment of hyperkalemia in renal failure with salbutamol inhalation. *J Intern Med* 228:35–37, 1990
25. McClure R, Prasad V, Brocklebank JT: Treatment of hyperkalemia using intravenous and nebulised salbutamol. *Arch Dis Child* 70:126–128, 1994
26. Mandelberg A, Krupnik Z, Houri S, Smetana S, et al.: Salbutamol metereddose inhaler with spacer for hyperkalemia: how fast? how safe? *Chest* 115:617–622, 1999
27. Sowinski K, Cronin D, Mueller B, Kraus M: Subcutaneous terbutaline use in CKD to reduce potassium concentrations. *Am J Kidney Dis* 45:1040–1045, 2005
28. Lens XM, Montoliu J, Cases A, Campistol JM, et al.: Treatment of hyperkalemia in renal failure: salbutamol v. insulin. *Nephrol Dial Transplant* 4:228–232, 1989
29. Allon M, Shanklin N: Adrenergic modulation of extrarenal potassium disposal in men with end-stage renal disease. *Kidney Int* 40:1103–1109, 1991
30. Iqbal Z, Friedman EA: Preferred therapy of hyperkalemia in renal insufficiency: survey of nephrology training-program directors (Letter). *N Engl J Med* 320:60–61, 1989
31. Fraley DS, Adler S: Correction of hyperkalemia by bicarbonate despite constant blood pH. *Kidney Int* 12:354–360, 1977
32. Blumberg A, Weidmann P, Ferrari P: Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. *Kidney Int* 41:369–374, 1992
33. Gutierrez R, Schlessinger F, Oster J, Rietberg B, et al.: Effect of hypertonic versus isotonic sodium bicarbonate on plasma potassium concentration in patients with end-stage renal disease. *Miner Electrolyte Metab* 17:297–302, 1991
34. Kim H-J: Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. *Nephron* 72:476–482, 1996
35. Allon M, Shanklin N: Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. *Am J Kidney Dis* 28:508–514, 1996
36. Johnson K, Cazee C, Gutch C, Ogden D: Sodium polystyrene sulfonate resin candy for control of potassium in chronic dialysis patients. *Clin Nephrol* 5:266–268, 1976
37. Flinn R, Merrill J, Welzant W: Treatment of the oliguric patient with a new sodium exchange resin and sorbitol; a preliminary report. *N Engl J Med* 264:111–115, 1961
38. Gruy-Kapral C, Emmet M, Santa Ana C, Porter J, et al.: Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *J Am Soc Nephrol* 9:1924–1930, 1998
39. Emmet M, Hootkins R, Fine K, Santa Ana C, et al.: Effect of three laxatives and a cation exchange resin on fecal sodium and potassium excretion. *Gastroenterology* 108:752–760, 1995
40. Lillemoe KD, Romol JL, Hamilton SR, Pennington LR, et al.: Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery* 101:266–272, 1987
41. Roy-Chaudhury P, Meisels I, Freedman S, Steinman T, et al.: Combined gastric and ileocecal toxicity (serpiginous ulcers) after oral Kayexalate in sorbitol therapy. *Am J Kidney Dis* 30:120–122, 1997
42. Hou S, McElroy P, Nootens J, Beach M: Safety and efficacy of low-potassium dialysate. *Am J Kidney Dis* 13:137–143, 1989
43. Dolson GM, Ellis KJ, Bernardo MV, Prakash R, et al.: Acute decreases in serum potassium augment blood pressure. *Am J Kidney Dis* 26:321–326, 1995
44. Zehnder C, Gutzwiller J-P, Huber A, Schindler C, et al.: Low-potassium and glucose-free dialysis maintains urea but enhances potassium removal. *Nephrol Dial Transplant* 16:78–84, 2001
45. Dolson G, Adrogue H: Low dialysate [K +] decreases efficiency of hemodialysis and increases urea rebound. *J Am Soc Nephrol* 9:2124–2128, 1998
46. Morrison G, Michelson E, Brown S, Morganroth J: Mechanism and prevention of cardiac arrhythmias in chronic hemodialysis patients. *Kidney Int* 17:811–819, 1980
47. Heguilen R, Scuriano C, Bellusci A, Fried P, et al.: The faster potassium-lowering effect of high dialysate bicarbonate concentrations in chronic haemodialysis patients. *Nephrol Dial Transplant* 20:591–597, 2005
48. Capdevila M, Martinez Ruiz I, Ferrer C, Monllor F, et al.: The efficiency of potassium removal during bicarbonate hemodialysis. *Hemodial Int* 9:296–302, 2005
49. Sherman RA, Hwang ER, Bernholc AS, Eisinger RP: Variability in potassium removal by hemodialysis. *Am J Nephrol* 6:284–288, 1986
50. Ward RA, Wathen RL, Williams TE, Harding GB: Hemodialysate composition and intradialytic metabolic, acid-base and potassium changes. *Kidney Int* 32:129–135, 1987
51. Gutzwiller J-P, Schneditz D, Huber A, Schindler C, et al.: Increasing blood flow increases [Kt/V(urea)] and potassium removal but fails to improve phosphate removal. *Clin Nephrol* 59:130–136, 2003
52. Allon M, Shanklin N: Effect of albuterol treatment on subsequent dialytic potassium removal. *Am J Kidney Dis* 26:607–613, 1995
53. Beto J, Bansal V: Medical nutrition therapy in chronic kidney failure: integrating clinical practice guidelines. *J Am Diet Assoc* 104:404–409, 2004
54. National Kidney Foundation. Potassium and your diet. Available at www.kidney.org, accessed on January 12, 2007
55. Gifford JD, Rutsky EA, Kirk KA, McDaniel HG: Control of serum potassium during fasting in end-stage renal disease. *Kidney Int* 35:90–94, 1989
56. Castellino P, Bia M, DeFronzo R: Adrenergic modulation of potassium metabolism in uremia. *Kidney Int* 37:793–798, 1990
57. Nowicki M, Miszczack KJ: Nonselective beta-adrenergic blockade augments fasting hyperkalemia in hemodialysis patients. *Nephron* 91:222–227, 2002
58. Horl M, Horl W: Drug therapy for hypertension in hemodialysis patients. *Semin Dial* 17:288–294, 2004
59. Agarwal R: Supervised atenolol therapy in the management of hemodialysis hypertension. *Kidney Int* 55:1528–1535, 1999
60. Mann J, Gerstein H, Pogue J, Bosch J, et al.: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 134:629–636, 2001
61. Efrati S, Zaidenstein R, Dishy V, Beberashvili I, et al.: ACE inhibitors and survival of hemodialysis patients. *Am J Kidney Dis* 40:1023–1029, 2002
62. Knoll G, Sahgal A, Nair R, Graham J, et al.: Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. *Am J Med* 112:110–114, 2002
63. Henry M, Amor M, Beyar R, Henry I, et al.: Clinical experience with a new nitinol self-expanding stent in peripheral arteries. *J Endovasc Surg* 3:369–379, 1996
64. Saudan P, Mach F, Perneger T, Schnetzler B, et al.: Safety of low-dose sprionolactone administration in chronic haemodialysis patients. *Nephrol Dial Transplant* 18:2359–2363, 2003
65. Hussain S, Dreyfus D, Marcus R, Biederman R, et al.: Is spironolactone safe for dialysis patients? *Nephrol Dial Transplant* 18:2364–2368, 2003
66. Singhal P, Desroches L, Mattana J, Abramovici M, et al.: Mineralocorticoid therapy lowers serum potassium in patients with end-stage renal disease. *Am J Nephrol* 13:138–141, 1993
67. Furuya R, Kumagai H, Sakao T, Maruyama Y, et al.: Potassium-lowering effect of mineralocorticoid therapy in patients undergoing hemodialysis. *Nephron* 92:576–581, 2002
68. Kaisar M, Wiggins K, Sturtevant J, Hawley C, et al.: A randomized controlled trial of fludrocortisone for the treatment of hyperkalemia in hemodialysis patients. *Am J Kidney Dis* 47:809–814, 2006
69. Mathialahan T, Sandle G: Dietary potassium and laxatives as regulators of colonic potassium secretion in end-stage renal disease. *Nephrol Dial Transplant* 18:341–347, 2003
70. Mousa J, Rassoul Z, Popovich W, Hassan A, et al.: A new treatment for interdialytic hyperkalemia—the use of fosinopril sodium. *Am J Nephrol* 19:395–399, 1999
71. De Nicola L, Bellizzi V, Minutolo R, Cioffi M, et al.: Effect of dialysate sodium concentration on interdialytic increase of potassium. *J Am Soc Nephrol* 11:2337–2343, 2000
72. Allon M: Medical and dialytic management of hyperkalemia in hemodialysis patients. *Int J Artif Organs* 19:697–699, 1996