

Management of severe hyperkalemia

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Background and Objectives: Hyperkalemia is one of the few potentially lethal electrolyte disturbances. Prompt recognition and expeditious treatment of severe hyperkalemia are expected to save lives. This review is intended to provide intensivists and other interested clinicians with an understanding of the pathophysiology that underlies hyperkalemia, and a rational approach to its management.

Methods: This article reviews and analyzes literature relevant to the pathophysiology and management of severe hyperkalemia. Methods include search of MEDLINE, and bibliographic search of current textbooks and journal articles.

Results and Conclusions: A more complete understanding of potassium homeostasis in recent years has led to new approaches to the management of severe hyperkalemia. The physiologically based sequential approach still applies. The efficacy, pitfalls, and risks of the agents available for use at each step in the sequence are critically reviewed. Rational use of the available tools will allow clinicians to successfully treat severe hyperkalemia. (Crit Care Med 2008; 36:3246–3251)

KEY WORDS: hyperkalemia; treatment; critical illness

Hyperkalemia is common in hospitalized patients, and may be associated with adverse clinical outcomes (1, 2). Its prevalence and clinical impact in critically ill patients are unknown. There is no doubt, however, that severe hyperkalemia can be fatal. Proper treatment of hyperkalemia depends on an understanding of the underlying physiology.

The ratio of extracellular to intracellular potassium (K) concentration largely determines the cell membrane resting electrical potential that, in turn, regulates the function of excitable tissues (cardiac and skeletal muscle, and nerve) (1). Small absolute changes in the extracellular K concentration will have large effects on that ratio, and consequently on the function of excitable tissues. Thus, it is not surprising that the plasma K concentration (P_K) normally is maintained within very narrow limits. This tight regulation is accomplished by two cooperative systems. One system defends against short-term changes in P_K by regulating internal balance: the equilibrium of K across the cell membrane. This equilib-

rium is modulated by insulin (3–5), catecholamines (6, 7) and, to a lesser extent, by acid-base balance (8–10), plasma tonicity, and several other factors (3). The other system governs K homeostasis over the long-term by regulating external balance: the parity between K intake and elimination. In individuals with normal renal function, the kidneys are responsible for elimination of about 95% of the daily K load with the remainder exiting through the gut. External K balance is maintained largely by modulating renal K elimination.

Almost all the K excreted by the kidney comes from K secreted in the distal nephron (connecting tubule and collecting duct) (11). Virtually all regulation of K excretion takes place at this site in the nephron, under the influence of two principle factors: the rate of flow and solute (sodium and chloride) delivery through that part of the nephron; and the effect of aldosterone (11). K secretion is directly proportional to flow rate and sodium delivery through the lumen of the distal nephron, and to circulating aldosterone levels in the setting of an aldosterone-sensitive epithelium. This explains, in part, why the use of diuretic drugs that work proximal to the K secretory site (loop and thiazide diuretics) often is accompanied by hypokalemia. K secretion is inversely proportional to the chloride concentration of the luminal fluid and is stimulated, for example, by luminal delivery of sodium bicarbonate (12). Conversely, hyperkalemia commonly accom-

panies acute kidney injury, particularly in the setting of mineralocorticoid deficiency (13–15). Such mineralocorticoid deficiency is often induced by drugs that interfere with the renin-angiotensin-aldosterone axis and commonly causes hyperkalemia in patients with chronic kidney disease, as well (16, 17). Sustained hyperkalemia is always attributable to inadequate renal K elimination. A detailed discussion of the causes of hyperkalemia in critically ill patients is beyond the scope of this article, but may be found in a recent review (18).

Clinical Manifestations of Hyperkalemia

Alterations in P_K have a variety of adverse clinical consequences, the expression of which may be magnified in the critically ill patient. The most serious of these manifestations are those involving excitable tissues.

Cardiac Effects. Hyperkalemia depolarizes the cell membrane, slows ventricular conduction, and decreases the duration of the action potential. These changes produce the classic electrocardiographic (EKG) manifestations of hyperkalemia including (in order of their usual appearance) peaked T waves, widening of the QRS complex, loss of the P wave, “sine wave” configuration, or ventricular fibrillation and asystole (19, 20). These EKG changes may be modified by a multitude of factors such as extracellular fluid pH, calcium concentration, sodium concentration, and the rate of rise of P_K

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Table 1. Emergency treatment of hyperkalemia

Agent	Dose	Onset	Duration	Complications
Membrane stabilization				
Calcium gluconate (10%)	10 mL IV over 10 min	Immediate	30–60 min	Hypercalcemia Volume overload hypertonicity
Hypertonic (3%) sodium chloride	50 mL IV push	Immediate	Unknown	
Redistribution				
Insulin (short acting)	10 units IV push, with 25–40 g dextrose (50% solution)	20 min	4–6 hrs	hypoglycemia
Albuterol	20 mg in 4 mL normal saline solution, nebulized over 10 min	30 min	2 hrs	Tachycardia inconsistent response
Elimination				
Loop diuretics				
Furosemide	40–80 mg IV	15 min	2–3 hrs	Volume depletion
Bumetanide	2–4 mg IV			
Sodium bicarbonate	150 mmol/L IV at variable rate	Hours	Duration of infusion	Metabolic alkalosis volume overload
Sodium polystyrene sulfonate (Kayexalate, Kionex)	15–30 g in 15–30 mL (70% sorbitol orally)	>2 hrs	4–6 hrs	Variable efficacy intestinal necrosis
Hemodialysis		Immediate	3 hrs	Arrhythmias (?)

IV, intravenously.

(19). Hospitalized patients with hyperkalemia are reported to have a higher mortality rate than those without hyperkalemia (21, 22), but the high prevalence of coexistent renal insufficiency in this population is a significant confounding variable that prevents attribution of the increased mortality to the hyperkalemia itself.

EKG changes may not accompany changes in P_K . The sensitivity of the electrocardiogram to reveal changes of hyperkalemia is quite low (23). It does increase in proportion to the severity of the hyperkalemia (23), but normal electrocardiograms have been seen even with extreme hyperkalemia (24) and the first cardiac manifestation of hyperkalemia may be ventricular fibrillation (25). (The explanation for a normal electrocardiogram in the setting of extreme hyperkalemia is not entirely clear, but may relate to a slow rate of rise in the P_K [20, 24]). Given this insensitivity of the electrocardiogram, EKG changes should not be considered necessary for the emergency treatment of severe hyperkalemia.

Neuromuscular Effects. Hyperkalemia may result in paraesthesias and weakness progressing to a flaccid paralysis, which typically spares the diaphragm. Deep tendon reflexes are depressed or absent. Cranial nerves are rarely involved and sensory changes are minimal (26, 27).

Metabolic Effects. Hyperkalemia decreases renal ammoniogenesis which by itself may produce a mild hyperchloremic metabolic acidosis (28), and will limit the kidney's ability to excrete an acid load

and, thus, prevent correction of a metabolic acidosis (29).

Treatment of Severe Hyperkalemia

In general, the initial treatment of severe hyperkalemia is independent of the cause of the disturbance, whereas the rational therapy of chronic hyperkalemia depends on an understanding of its pathogenesis.

In considering when hyperkalemia constitutes an emergency, several points should be kept in mind. First, the electrophysiologic effects of hyperkalemia are directly proportional to both the absolute P_K and its rate of rise (19). Second, concurrent metabolic disturbances may ameliorate (e.g., hyponatremia, hypercalcemia, alkalemia) or exacerbate (e.g., hyponatremia, hypocalcemia, acidemia) the electrophysiologic consequences of hyperkalemia (20, 24). Third, although the EKG manifestations of hyperkalemia are generally progressive and proportional to the P_K , ventricular fibrillation may be the first EKG disturbance of hyperkalemia (25); conversely, a normal EKG may be seen even with extreme hyperkalemia (24).

With this in mind, it is apparent that neither the EKG nor the P_K alone is an adequate index of the urgency of hyperkalemia, and that the clinical context must be considered when assessing a hyperkalemic patient. Thus, any pronouncement on an absolute P_K value constituting an emergency must be seen

as arbitrary. Nonetheless, since the treatment for acute hyperkalemia is safe if applied properly and hyperkalemia is potentially and unpredictably lethal, it is prudent to maintain a low threshold for instituting emergency therapy. Because most patients manifest hyperkalemic EKG changes at P_K greater than 6.7 mmol/L (20), hyperkalemia should be treated emergently for 1) $P_K > 6.5$ mmol/L or 2) EKG manifestations of hyperkalemia regardless of the P_K (30).

Therapy of acute or severe hyperkalemia is directed at preventing or ameliorating its untoward electrophysiologic effects on the myocardium. The goals of therapy, in chronologic order, are as follows (Table 1):

1. Antagonize the effect of K on excitable cell membranes.
2. Redistribute extracellular K into cells.
3. Enhance elimination of K from the body.

Membrane Antagonism

Calcium. Calcium directly antagonizes the myocardial effects of hyperkalemia without lowering P_K (31, 32). It does so by reducing the threshold potential of cardiac myocytes, thereby restoring the normal gradient with the resting membrane potential, which is distorted by hyperkalemia (19, 20, 33). Calcium is beneficial even in patients who are normocalcemic. Calcium for injection is available as the chloride or gluconate salt, both 10% by weight. The preferred

agent is the gluconate salt, since it is less likely than calcium chloride to cause tissue necrosis if it extravasates (34). The recommended dose is 10 mL intravenous over 10 mins. The onset of action is <3 mins. The EKG should be monitored continuously. The dose may be repeated in 5 mins if there is no improvement in the EKG, or if the EKG deteriorates after an initial improvement. The duration of action is 30–60 mins, during which time further measures may be undertaken to lower P_K (30).

There are several case reports of sudden death in patients given intravenous calcium while also receiving digitalis glycosides (35, 36). Although these anecdotes do not provide clear guidance, it is wise to administer intravenous calcium under very close supervision to patients known or strongly suspected to have toxic levels of digitalis glycosides.

Hypertonic Saline. Intravenous hypertonic sodium chloride has been shown to reverse the EKG changes of hyperkalemia in patients with concurrent hyponatremia (37). This effect seems to be mediated by a change in the electrical properties of cardiomyocytes rather than by a reduction in P_K (38). Whether hypertonic saline is effective in the treatment of eunatremic patients has not been established. Until such benefit has been demonstrated, the use of hypertonic (3%) saline should be restricted to hyponatremic patients with hyperkalemia, with an awareness of the volume overload that may ensue.

Redistribution of Potassium into Cells

Insulin. Insulin reliably lowers P_K in patients with end-stage renal disease (39–43), confirming its effect to shift K into cells. The effect of insulin on potassium is dose dependent from the physiologic through the pharmacologic range (5). It is mediated by activation of Na, K-ATPase, apparently by recruitment of intracellular pump components into the plasma membrane (4, 44). An intravenous dose of ten units of regular insulin given as a bolus along with an intravenous bolus of dextrose (25 g as a 50% solution) to anephric adult patients lowers the P_K by about 0.6 mmol/L (42). The onset of action is <15 mins and the effect is maximal between 30 and 60 mins after a single bolus (41, 42). After the initial bolus, a dextrose infusion should be started, since a single bolus of 25 g of

dextrose has been shown to be inadequate to prevent hypoglycemia at 60 mins (42). It is interesting to note that when insulin was given by continuous intravenous infusion for 4 hrs to normal volunteers, P_K fell over the first 90 mins and rose thereafter (45). Based on that observation, there seems to be no advantage of a continuous infusion over a bolus injection.

Insulin should be used without dextrose in hyperglycemic patients; indeed, the cause of the hyperkalemia in those patients may be the hyperglycemia itself (46). The administration of hypertonic dextrose alone for hyperkalemia is not recommended for two reasons: first, endogenous insulin levels are unlikely to rise to the level necessary for a therapeutic effect; and second, there is a risk of exacerbating the hyperkalemia by inducing hypertonicity (46).

β -adrenoceptor Agonists. An appreciation for the effect of catecholamines on internal potassium balance recently has been applied to the clinic. Patients with renal failure given the selective β_2 -adrenoceptor agonist, albuterol, by intravenous infusion (0.5 mg over 15 mins) show a significant decline in P_K (about 1 mmol/L) that is maximal between 30 and 60 mins (47). Because injectable albuterol is unavailable in the United States, it is encouraging to note that nebulized albuterol in a high dose, administered to patients with end-stage renal disease, has a similar effect: P_K declines by 0.6 mmol/L after inhalation of 10 mg of albuterol, and by about 1.0 mmol/L after 20 mg (41, 42, 48, 49). Note that the effective dose is at least four times higher than that typically used for bronchodilation (50), although a smaller decline in P_K (about 0.4 mmol/L after 60 mins) is seen even with a metered-dose inhaler (51). The effect of high-dose therapy is apparent at 30 mins and persists for at least 2 hrs (48). The effect of insulin is additive with that of albuterol, with the combination reported to result in a decline in P_K by about 1.2 mmol/L at 60 mins (42). More recently, subcutaneous terbutaline (7 μ g/kg body weight) has been shown to reduce P_K in selected dialysis patients by an average of 1.3 mmol/L within 60 mins (52). Mild tachycardia is the most common reported side effect of high-dose nebulized albuterol or terbutaline. Patients taking nonselective β -adrenoceptor blockers will be unlikely to manifest the hypokalemic effect of albuterol. Even among patients not taking β -blockers, as many as 40% seem to be resistant to the

hypokalemic effect of albuterol (42, 48). The mechanism for this resistance is unknown, and there is currently no basis for predicting which patients will respond. For that reason, albuterol should never be used as a single agent for the treatment of urgent hyperkalemia in patients with renal failure.

Bicarbonate. The putative benefits of a bolus injection of sodium bicarbonate in the emergency treatment of hyperkalemia pervaded the literature until the past decade. Ironically, this dogma was based on studies using a prolonged (4–6 hrs) infusion of bicarbonate (53). It has now been clearly demonstrated that short-term bicarbonate infusion does not reduce P_K in patients with dialysis-dependent kidney failure, implying that it does not cause K shift into cells. Infusion of a hypertonic or an isotonic bicarbonate solution for 60 mins has been shown to have no effect on P_K in dialysis patients, despite a substantial increase in serum bicarbonate concentration (40, 54–56). Only after a 4-hr infusion was a small (0.6 mmol/L) but significant decrease in P_K is detectable (57). Whether bicarbonate infusion might enhance insulin-mediated cellular K uptake remains unresolved by two contradictory studies (54, 56). The absence of a demonstrable effect of bicarbonate to shift K into cells over the short term is not to imply that bicarbonate might not be useful in the emergency treatment of hyperkalemia; rather, that its onset and mechanism of action are quite different from what conventional wisdom has held (see below). Furthermore, the foregoing is not meant to imply that sodium bicarbonate should be withheld from the hyperkalemic patient with metabolic acidosis; rather, that no short-term effect on the P_K should be anticipated.

Elimination of Potassium from the Body

Enhanced Renal Elimination. Hyperkalemia occurs most often in patients with renal insufficiency. However, renal K excretion may be enhanced even in patients with significant renal impairment by increasing the delivery of solute to the distal nephron, the site of K secretion.

Studies using acetazolamide show that bicarbonate delivery to this site in the nephron has a particular kaliuretic effect (58), even in patients with renal insufficiency (59). It would be unwise to

administer acetazolamide alone to most patients with hyperkalemia, since they tend to present with a concomitant metabolic acidosis that would be exacerbated by the drug. But a sodium bicarbonate infusion administered during 4–6 hrs at a rate designed to alkalinize the urine may enhance urinary K excretion (53), and would be desirable especially in patients with metabolic acidosis. The risk of volume expansion with the bicarbonate infusion can be mitigated by the use of loop-acting diuretics, which would be likely to further enhance the kaliuretic effect. Loop-acting diuretics alone or in combination with a thiazide diuretic will induce a kaliuresis and will be beneficial in the volume expanded patient. Diuretic-induced volume contraction must be avoided since this will lead to decreased distal nephron flow and reduced K excretion (30).

Exchange Resin. Sodium polystyrene sulfonate (SPS, Kayexalate, Kionex) is a cation-exchange resin that is prepared in the sodium phase but has a higher affinity for potassium than sodium (60). In the lumen of the intestine, it exchanges sodium for secreted potassium. Most of this exchange takes place in the colon, the site of most potassium secretion in the gut (61, 62). Each gram of resin binds approximately 0.65 mmol of potassium *in vivo*, although the effect is highly variable and unpredictable (63). The resin causes constipation and, hence, almost always is given with a cathartic. It may be given orally or by retention enema, although the oral route is considered to be more effective because of the longer transit time through the gut lumen (3).

There are two concerns with the use of SPS for the treatment of urgent hyperkalemia. The first is its slow effect. When given orally, the onset of action is at least 2 hrs and the maximum effect may not be seen for 6 hrs or more (60). The effect of SPS as a retention enema is more rapid but of lesser magnitude. One recent study in normokalemic hemodialysis patients failed to show any effect on P_K during 12 hrs after an oral dose of 30 g of SPS with cathartic (64). Indeed, early studies with this agent showed very little effect over and above that of sorbitol alone (60). The second concern with SPS is its possible toxicity. There are numerous case reports of patients who have developed intestinal necrosis after exposure to SPS in sorbitol as an enema (63, 65–69), and as an oral agent (66, 70–74). A retrospective study estimated the prevalence of colonic necrosis to

be 1.8% among postoperative patients receiving SPS (75). Thus, the slow onset of action and serious, albeit infrequent, toxicity make SPS a poor choice for the treatment of urgent hyperkalemia.

Dialysis. Hemodialysis is the method of choice for removal of potassium from the body. P_K falls by over 1 mmol/L in the first 60 mins of hemodialysis and a total of 2 mmol/L by 180 mins, after which it reaches a plateau (3, 76). Rebound always occurs after dialysis, with 35% of the reduction abolished after an hour and nearly 70% after 6 hr; the magnitude of the postrebound P_K is proportional to the predialysis P_K (77). There is controversy as to whether dialysis for severe hyperkalemia precipitates serious ventricular arrhythmias (78–84). Because of that possibility, patients dialyzed for severe hyperkalemia should have continuous EKG monitoring (3).

The rate of potassium removal with peritoneal dialysis is much slower than with hemodialysis. Indeed, much of the decrement in P_K with peritoneal dialysis seems to be due to translocation of potassium into cells as a result of the glucose load rather than extracorporeal disposal. This modality may be used for patients on maintenance peritoneal dialysis who have modest hyperkalemia (3).

CONCLUSION

Hyperkalemia is one of the few potentially lethal electrolyte disorders. Its rational treatment has evolved as a result of our more complete understanding of the physiology of potassium homeostasis. The sequential approach to the treatment of urgent hyperkalemia still pertains. Calcium gluconate is the preferred agent to immediately reverse the adverse electrophysiologic effects of hyperkalemia, although hypertonic saline may be used in selected circumstances. Insulin is the most reliable agent for translocating K into cells, but β -adrenoceptor agonists provide some additional benefit in about 60% of patients. Terbutaline may have some utility in this regard, but its use has never been studied in patients with heart disease. β -adrenoceptor agonists should never be used without insulin for this purpose, since about 40% of patients will have no response. Sodium bicarbonate seems to have no effect to shift K into cells, even after several hours. It is likely to be effective, especially in combination with a diuretic drug, in enhancing urinary K elimination in patients with some

kidney function, although its use for this purpose has not been systematically evaluated. SPS resin has a slow onset of action and debatable efficacy. Furthermore, it carries the small risk of intestinal necrosis. Hemodialysis remains the most reliable tool for removing K from the body in patients with kidney failure.

REFERENCES

1. Gennari FJ: Disorders of potassium homeostasis. Hypokalemia and hyperkalemia. *Crit Care Clin* 2002; 18:273–288, vi
2. Stevens MS, Dunlay RW: Hyperkalemia in hospitalized patients. *Int Urol Nephrol* 2000; 32:177–180
3. Ahmed J, Weisberg LS: Hyperkalemia in dialysis patients. *Semin Dial* 2001; 14:348–356
4. Clausen T, Everts ME: Regulation of the Na, K-pump in skeletal muscle. *Kidney Int* 1989; 35:1–13
5. DeFronzo RA, Felig P, Ferrannini E, et al: Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. *Am J Physiol* 1980; 238:E421–E427
6. DeFronzo RA, Bia M, Birkhead G: Epinephrine and potassium homeostasis. *Kidney Int* 1981; 20:83–91
7. Rosa RM, Silva P, Young JB, et al: Adrenergic modulation of extrarenal potassium disposal. *N Engl J Med* 1980; 302:431–434
8. Adrogué HJ, Madias NE: Changes in plasma potassium concentration during acute acid-base disturbances. *Am J Med* 1981; 71:456–467
9. Magner PO, Robinson L, Halperin RM, et al: The plasma potassium concentration in metabolic acidosis: A re-evaluation. *Am J Kidney Dis* 1988; 11:220–224
10. Perez GO, Oster JR, Vaamonde CA: Serum potassium concentration in acidemic states. *Nephron* 1981; 27:233–243
11. Mount DB, Yu ASL: Transport of inorganic solutes: Sodium, chloride, potassium, magnesium, calcium and phosphorus. In: Brenner and Rector's *The Kidney*. Brenner B (Ed). Eighth Edition. Philadelphia, Saunders, 2007, pp 181–183
12. Velazquez H, Ellison DH, Wright FS: Luminal influences on potassium secretion: Chloride, sodium, and thiazide diuretics. *Am J Physiol* 1992; 262:F1076–F1082
13. Dunn MJ: Nonsteroidal antiinflammatory drugs and renal function. *Annu Rev Med* 1984; 35:411–428
14. Mathews A, Bailie GR: Acute renal failure and hyperkalemia associated with triamterene and indomethacin. *Vet Hum Toxicol* 1986; 28:224–225
15. Paladini G, Tonazzi C: Indomethacin-induced hyperkalemia and renal failure in multiple myeloma. *Acta Haematol* 1982; 68:256–260
16. Juurlink DN, Mamdani MM, Lee DS, et al: Rates of hyperkalemia after publication of

- the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; 351:543–551
17. Palmer BF: Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004; 351: 585–592
 18. Faridi AB, Weisberg LS: Acid-base, electrolyte and metabolic abnormalities. In: *Critical Care Medicine: Principles of Diagnosis and Management in Adults*. Parrillo JE, Dellinger RP (Eds). Third Edition. Philadelphia, Elsevier, 2008, pp 1203–1243
 19. Fisch C: Relation of electrolyte disturbances to cardiac arrhythmias. *Circulation* 1973; 47: 408–419
 20. Surawicz B: Electrolytes and the electrocardiogram. *Postgrad Med* 1974; 55:123–129
 21. Moore ML, Bailey RR: Hyperkalaemia in patients in hospital. *N Z Med J* 1989; 102: 557–558
 22. Paice B, Gray JM, McBride D, et al: Hyperkalaemia in patients in hospital. *Br Med J (Clin Res Ed)* 1983; 286:1189–1192
 23. Montague BT, Ouellette JR, Buller GK: Retrospective review of the frequency of ECG changes in hyperkalemia. *Clin J Am Soc Nephrol* 2008; 3:324–330
 24. Szerlip HM, Weiss J, Singer I: Profound hyperkalemia without electrocardiographic manifestations. *Am J Kidney Dis* 1986; 7:461–465
 25. Dodge HT, Grant RP, Seavey PW: The effect of induced hyperkalemia on the normal and abnormal electrocardiogram. *Am Heart J* 1953; 45:725–740
 26. Weiner ID, Wingo CS: Hyperkalemia: A potential silent killer. *J Am Soc Nephrol* 1998; 9:1535–1543
 27. Weiner M, Epstein FH: Signs and symptoms of electrolyte disorders. *Yale J Biol Med* 1970; 43:76–109
 28. Tannen RL: Relationship of renal ammonia production and potassium homeostasis. *Kidney Int* 1977; 11:453–465
 29. Szymlan P, Better OS, Chaimowitz C, et al: Role of hyperkalemia in the metabolic acidosis of isolated hypoaldosteronism. *N Engl J Med* 1976; 294:361–365
 30. Weisberg LS: Potassium homeostasis. In: *Principles and Practice of Medical Intensive Care*. Carlson RW, Geheb MA (Eds). Philadelphia, Saunders, 1993
 31. Bisogno JL, Langley A, Von Dreele MM: Effect of calcium to reverse the electrocardiographic effects of hyperkalemia in the isolated rat heart: A prospective, dose-response study. *Crit Care Med* 1994; 22:697–704
 32. Chamberlain MJ: Emergency treatment of hyperkalaemia. *Lancet* 1964; 18:464–467
 33. Ettinger PO, Regan TJ, Oldewurtel HA: Hyperkalemia, cardiac conduction, and the electrocardiogram: A review. *Am Heart J* 1974; 88:360–371
 34. Semple P, Booth C: Calcium chloride; a reminder. *Anaesthesia* 1996; 51:93
 35. Bower J, Mengle H: The additive effect of calcium and digitalis. A warning with a report of two deaths. *JAMA* 1936; 106: 1151–1153
 36. Shrager MW: Digitalis intoxication; a review and report of forty cases, with emphasis on etiology. *AMA Arch Intern Med* 1957; 100: 881–893
 37. Garcia-Palmieri MR: Reversal of hyperkalemic cardiotoxicity with hypertonic saline. *Am Heart J* 1962; 64:483–488
 38. Ballantyne F III, Davis LD, Reynolds EW Jr, et al: Cellular basis for reversal of hyperkalemic electrocardiographic changes by sodium. *Am J Physiol* 1975; 229:935–940
 39. Sterns RH, Feig PU, Pring M, et al: Disposition of intravenous potassium in anuric man: A kinetic analysis. *Kidney Int* 1979; 15: 651–660
 40. Blumberg A, Weidmann P, Shaw S, et al: Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med* 1988; 85:507–512
 41. Lens XM, Montoliu J, Cases A, et al: Treatment of hyperkalaemia in renal failure: Salbutamol v. insulin. *Nephrol Dial Transplant* 1989; 4:228–232
 42. Allon M, Copkney C: Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int* 1990; 38:869–872
 43. Allon M, Takeshian A, Shanklin N: Effect of insulin-plus-glucose infusion with or without epinephrine on fasting hyperkalemia. *Kidney Int* 1993; 43:212–217
 44. Hundal HS, Marette A, Mitsumoto Y, et al: Insulin induces translocation of the alpha 2 and beta 1 subunits of the Na⁺/K⁺-ATPase from intracellular compartments to the plasma membrane in mammalian skeletal muscle. *J Biol Chem* 1992; 267:5040–5043
 45. Minaker KL, Rowe JW: Potassium homeostasis during hyperinsulinemia: Effect of insulin level, beta-blockade, and age. *Am J Physiol* 1982; 242:E373–E377
 46. Goldfarb S, Cox M, Singer I, et al: Acute hyperkalemia induced by hyperglycemia: Hormonal mechanisms. *Ann Intern Med* 1976; 84:426–432
 47. Montoliu J, Lens XM, Revert L: Potassium-lowering effect of albuterol for hyperkalemia in renal failure. *Arch Intern Med* 1987; 147: 713–717
 48. Allon M, Dunlay R, Copkney C: Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; 110: 426–429
 49. Montoliu J, Almirall J, Ponz E, et al: Treatment of hyperkalaemia in renal failure with salbutamol inhalation. *J Intern Med* 1990; 228:35–37
 50. Nair S, Thomas E, Pearson SB, et al: A randomized controlled trial to assess the optimal dose and effect of nebulized albuterol in acute exacerbations of COPD. *Chest* 2005; 128:48–54
 51. Mandelberg A, Krupnik Z, Houry S, et al: Salbutamol metered-dose inhaler with spacer for hyperkalemia: How fast? how safe? *Chest* 1999; 115:617–622
 52. Sowinski KM, Cronin D, Mueller BA, et al: Subcutaneous terbutaline use in CKD to reduce potassium concentrations. *Am J Kidney Dis* 2005; 45:1040–1045
 53. Fraley DS, Adler S: Correction of hyperkalemia by bicarbonate despite constant blood pH. *Kidney Int* 1977; 12:354–360
 54. Allon M, Shanklin N: Effect of bicarbonate administration on plasma potassium in dialysis patients: Interactions with insulin and albuterol. *Am J Kidney Dis* 1996; 28:508–514
 55. Gutierrez R, Schlessinger F, Oster JR, et al: Effect of Hypertonic versus isotonic sodium-bicarbonate on plasma potassium concentration in patients with end-stage renal-disease. *Miner Electrolyte Metab* 1991; 17:297–302
 56. Kim HJ: Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. *Nephron* 1996; 72:476–482
 57. Blumberg A, Weidmann P, Ferrari P: Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. *Kidney Int* 1992; 41:369–374
 58. Carlisle EJ, Donnelly SM, Ethier JH, et al: Modulation of the secretion of potassium by accompanying anions in humans. *Kidney Int* 1991; 39:1206–1212
 59. Kamel KS, Ethier JH, Quaggin S, et al: Studies to determine the basis for hyperkalemia in recipients of a renal transplant who are treated with cyclosporine. *J Am Soc Nephrol* 1992; 2:1279–1284
 60. Scherr L, Ogden DA, Mead AW, et al: Management of hyperkalemia with a cation-exchange resin. *N Engl J Med* 1961; 264: 115–119
 61. Frohner PP, Johnson WJ, Mueller GJ, et al: Resin treatment of hyperkalemia. II. Clinical experience with a cation exchange resin (calcium cycle). *J Lab Clin Med* 1968; 71: 840–846
 62. Frohner PP, Johnson WJ, Mueller GJ, et al: Resin treatment of hyperkalemia. I. Exchange properties of a cation exchange resin (calcium cycle). *J Lab Clin Med* 1968; 71: 834–839
 63. Lillemo KD, Romolo JL, Hamilton SR, et al: Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: Clinical and experimental support for the hypothesis. *Surgery* 1987; 101:267–272
 64. Gruy-Kapral C, Emmet M, Santa Nan CA, et al: Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *J Am Soc Nephrol* 1998; 9:1924–1930
 65. Rogers FB, Li SC: Acute colonic necrosis associated with sodium polystyrene sulfonate (Kayexalate) enemas in a critically ill patient: Case report and review of the literature. *J Trauma* 2001; 51:395–397
 66. Rashid A, Hamilton SR: Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (kayexalate) in sorbitol: An underrecognized condition. *Am J Surg Pathol* 1997; 21:60–69
 67. Scott TR, Graham SM, Schweitzer EJ, et al:

- Colonic necrosis following sodium polystyrene sulfonate (kayexalate)-sorbitol enema in a renal transplant patient. Report of a case and review of the literature. *Dis Colon Rectum* 1993; 36:607–609
68. Wootton FT, Rhodes DF, Lee WM, et al: Colonic necrosis with kayexalate-sorbitol enemas after renal transplantation. *Ann Intern Med* 1989; 111:947–949
 69. Chatelain D, Brevet M, Manaouil D, et al: Rectal stenosis caused by foreign body reaction to sodium polystyrene sulfonate crystals (kayexalate). *Ann Diagn Pathol* 2007; 11: 217–219
 70. Abraham SC, Bhagavan BS, Lee LA, et al: Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: Clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol* 2001; 25:637–644
 71. Cheng ES, Stringer KM, Pegg SP: Colonic necrosis and perforation following oral sodium polystyrene sulfonate (resonium A/kayexalate) in a burn patient. *Burns* 2002; 28:189–190
 72. Dardik A, Moesinger RC, Efron G, et al: Acute abdomen with colonic necrosis induced by kayexalate-sorbitol. *South Med J* 2000; 93: 511–513
 73. Gardiner GW: Kayexalate (sodium polystyrene sulfonate) in sorbitol associated with intestinal necrosis in uremic patients. *Can J Gastroenterol* 1997; 11:573–577
 74. Roy-Chaudhury P, Meisels IS, Freedman S, et al: Combined gastric and ileocecal toxicity (serpiginous ulcers) after oral kayexalate in sorbitol therapy. *Am J Kidney Dis* 1997; 30: 120–122
 75. Gerstman BB, Kirkman R, Platt R: Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *Am J Kidney Dis* 1992; 20: 159–161
 76. Blumberg A, Roser HW, Zehnder C, et al: Plasma potassium in patients with terminal renal failure during and after haemodialysis; relationship with dialytic potassium removal and total body potassium. *Nephrol Dial Transplant* 1997; 12:1629–1634
 77. Zehnder C, Gutzwiller JP, Huber A, et al: Low-potassium and glucose-free dialysis maintains urea but enhances potassium removal. *Nephrol Dial Transplant* 2001; 16: 78–84
 78. Hou S, McElroy PA, Nootens J, et al: Safety and efficacy of low-potassium dialysate. *Am J Kidney Dis* 1989; 13:137–143
 79. Karnik JA, Young BS, Lew NL, et al: Cardiac arrest and sudden death in dialysis units. *Kidney Int* 2001; 60:350–357
 80. Kovesdy CP, Regidor DL, Mehrotra R, et al: Serum and dialysate potassium concentrations and survival in hemodialysis patients. *Clin J Am Soc Nephrol* 2007; 2:999–1007
 81. Lafrance JP, Nolin L, Senecal L, et al: Predictors and outcome of cardiopulmonary resuscitation (CPR) calls in a large haemodialysis unit over a seven-year period. *Nephrol Dial Transplant* 2006; 21:1006–1012
 82. Morrison G, Michelson EL, Brown S, et al: Mechanism and prevention of cardiac arrhythmias in chronic hemodialysis patients. *Kidney Int* 1980; 17:811–819
 83. Redaelli B, Locatelli F, Limido D, et al: Effect of a new model of hemodialysis potassium removal on the control of ventricular arrhythmias. *Kidney Int* 1996; 50: 609–617
 84. Sforzini S, Latini R, Mingardi G, et al: Ventricular arrhythmias and four-year mortality in haemodialysis patients. Gruppo Emodialisi e Patologie Cardiovascolari. *Lancet* 1992; 339:212–213