Treatment and prevention of hyperkalemia in adults

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Literature review current through: Feb 2018. | **This topic last updated:** Dec 18, 2017.

INTRODUCTION — Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or chronic kidney disease (CKD) and/or disorders or drugs that inhibit the renin-angiotensin-aldosterone system (RAAS). Therapy for hyperkalemia due to potassium retention is ultimately aimed at inducing potassium loss [1,2].

In some cases, the primary problem is movement of potassium out of the cells, even though the total body potassium may be reduced. Redistributive hyperkalemia most commonly occurs in uncontrolled hyperglycemia (eg, diabetic ketoacidosis or hyperosmolar hyperglycemic state). In these disorders, hyperosmolality and insulin deficiency are primarily responsible for the transcellular shift of potassium from the cells into the extracellular fluid, which can be reversed by the administration of fluids and insulin. Many of these patients have a significant deficit in whole body potassium and must be monitored carefully for the development of hypokalemia during therapy. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Potassium replacement'.)

The treatment and prevention of hyperkalemia will be reviewed here. The causes, diagnosis, and clinical manifestations of hyperkalemia are discussed separately. (See "Causes and evaluation of hyperkalemia in adults" and "Clinical manifestations of hyperkalemia in adults".)

DETERMINING THE URGENCY OF THERAPY — The urgency of treatment of hyperkalemia varies with the presence or absence of the symptoms and signs associated with hyperkalemia, the severity of the potassium elevation, and the cause of hyperkalemia.

Our approach to therapeutic urgency is as follows (algorithm 1):

- **Hyperkalemic emergency** − In general, the following patients should be considered to have a hyperkalemic emergency and should therefore be treated with rapidly acting therapies (ie, intravenous calcium, insulin, and glucose) in addition to therapies that

remove potassium from the body (such as hemodialysis, gastrointestinal potassium binders, or diuretics):

- Patients who have clinical signs or symptoms of hyperkalemia. The most serious manifestations of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias, including sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole. These manifestations usually occur when the serum potassium concentration is ≥7 mEq/L with chronic hyperkalemia, or possibly at lower levels in patients with an acute rise in serum potassium and/or underlying cardiac conduction disease. (See "Clinical manifestations of hyperkalemia in adults".)

  There are several characteristic electrocardiogram (ECG) abnormalities associated with hyperkalemia (figure 1). A tall peaked T wave with a shortened QT interval is the earliest change (waveform 1), followed by progressive lengthening of the PR interval and QRS duration (waveform 2). The P wave may disappear, and ultimately, the QRS widens further to a sine wave. Ventricular standstill with a flat line on the ECG ensues with complete absence of electrical activity. The progression and severity of ECG changes do not correlate well with the serum potassium concentration. Conduction abnormalities, such as bundle branch blocks and arrhythmias (sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole) may also occur in hyperkalemia. (See "Clinical manifestations of hyperkalemia in adults", section on 'ECG changes'.)

- Patients with severe hyperkalemia (serum potassium greater than 6.5 mEq/L), especially if there is concurrent tissue breakdown or gastrointestinal bleeding, even if there are no clinical signs or symptoms.

- Some patients with moderate hyperkalemia (>5.5 mEq/L) who have significant renal impairment and marked, ongoing tissue breakdown (eg, rhabdomyolysis or crush injury, tumor lysis syndrome), ongoing potassium absorption (eg, from substantial gastrointestinal bleeding), or a significant non-anion gap metabolic acidosis or respiratory acidosis. Tissue breakdown can release large amounts of potassium from cells, which can lead to rapid and substantial elevations in serum potassium. Potassium absorption from the blood in the gastrointestinal tract or soft tissues can produce similar rapid increases in the serum potassium. Patients with a non-gap acidosis or respiratory acidosis may develop severe hyperkalemia quickly if the acidosis worsens, or if they develop an additional superimposed metabolic or respiratory acidosis, particularly when renal function is impaired. (See "Crush-related acute kidney injury (acute renal failure)" and "Tumor lysis syndrome: Definition, pathogenesis, clinical manifestations, etiology and risk factors" and "Prevention and treatment of heme pigment-induced acute kidney injury" and "Potassium balance in acid-base disorders".)

- **Patients needing prompt therapy** − Some patients without a hyperkalemic emergency should, nonetheless, have their potassium lowered promptly (ie, within 6 to 12 hours). Such patients include hemodialysis patients who present outside of regular

dialysis hours, patients with marginal renal function and/or marginal urine output, or hyperkalemic patients who need to be optimized for surgery. Measures such as isotonic bicarbonate infusion, intravenous 5 percent dextrose in water infusion overnight (to stimulate insulin in a fasting patient), or hemodialysis may be appropriate in these settings. Additional measures can include oral potassium binders or kaliuresis induced by intravenous saline with diuretic therapy.

●**Patients who can have the potassium lowered slowly** − Most patients with hyperkalemia have chronic, mild (≤5.5 mEq/L) or moderate (5.5 to 6.5 mEq/L) elevations in serum potassium due to chronic kidney disease (CKD) or the use of medications that inhibit the renin-angiotensin-aldosterone system ([RAAS] or both). Such patients do not require urgent lowering of the serum potassium and can often be treated with dietary modification, use of diuretics (if otherwise appropriate), treatment of chronic metabolic acidosis, or reversal of factors that can cause hyperkalemia (eg, nonsteroidal anti-inflammatory drugs, hypovolemia). In some instances, drugs that inhibit the RAAS are reduced or discontinued, and drugs that remove potassium by gastrointestinal cation exchange are prescribed for chronic use.

PATIENTS WITH A HYPERKALEMIC EMERGENCY — Identifying patients who have a hyperkalemic emergency is presented above (algorithm 1). (See 'Determining the urgency of therapy' above.)

Treatment approach to hyperkalemic emergencies — Patients with a hyperkalemic emergency should receive (table 1):

●Intravenous calcium to antagonize the membrane actions of hyperkalemia (see 'Calcium' below)

●Intravenous insulin (typically given with intravenous glucose) to drive extracellular potassium into cells (see 'Insulin with glucose' below)

●Therapy to rapidly remove excess potassium from the body (ie, loop or thiazide diuretics if renal function is not severely impaired, a gastrointestinal cation exchanger, and/ordialysis [preferably hemodialysis] if renal function is severely impaired) (see 'Remove potassium from the body' below)

●Treatment of reversible causes of hyperkalemia, such as correcting hypovolemia and discontinuing drugs that increase the serum potassium (eg, nonsteroidal anti-inflammatory drugs, inhibitors of the renin-angiotensin-aldosterone system) (table 2 and table 3) (see "Causes and evaluation of hyperkalemia in adults" and 'Drug-induced hyperkalemia'below)

Intravenous calcium and insulin are rapidly acting treatments that provide time for the initiation of therapies that remove the excess potassium from the body (table 4).

Monitoring — Continuous cardiac monitoring and serial electrocardiograms (ECGs) are warranted in patients with hyperkalemia who require rapidly acting therapies. The serum potassium should be measured at one to two hours after the initiation of treatment. The timing of further measurements is determined by the serum potassium concentration and

the response to therapy. Patients who receive insulin, with or without dextrose, should undergo hourly glucose measurements for up to six hours in order to monitor for hypoglycemia.

Administer rapidly acting therapies

Calcium — Calcium directly antagonizes the membrane actions of hyperkalemia [3], while hypocalcemia increases the cardiotoxicity of hyperkalemia [4]. As discussed elsewhere, hyperkalemia-induced depolarization of the resting membrane potential leads to inactivation of sodium channels and decreased membrane excitability. (See "Clinical manifestations of hyperkalemia in adults", section on 'Pathogenesis'.)

The effect of intravenous calcium administration begins within minutes but is relatively short lived (30 to 60 minutes). As a result, calcium should not be administered as monotherapy for hyperkalemia but should rather be combined with therapies that drive extracellular potassium into cells. Administration of calcium can be repeated every 30 to 60 minutes if the hyperkalemic emergency persists and the serum calcium does not become elevated. (See 'Insulin with glucose' below.)

Calcium can be given as either calcium gluconate or calcium chloride. Calcium chloride contains three times the concentration of elemental calcium compared with calcium gluconate (13.6 versus 4.6 mEq in 10 mL of a 10 percent solution). However, calcium gluconate is generally preferred because calcium chloride may cause local irritation at the injection site.

The usual dose of calcium gluconate is 1000 mg (10 mL of a 10 percent solution) infused over two to three minutes, with constant cardiac monitoring. The usual dose of calcium chloride is 500 to 1000 mg (5 to 10 mL of a 10 percent solution), also infused over two to three minutes, with constant cardiac monitoring. The dose of either formulation can be repeated after five minutes if the ECG changes persist or recur.

Concentrated calcium infusions (particularly calcium chloride) are irritating to veins, and extravasation can cause tissue necrosis. As a result, a central or deep vein is preferred for administration of calcium chloride. Calcium gluconate can be given peripherally, ideally through a small needle or catheter in a large vein. Calcium should **not** be given in bicarbonate-containing solutions, which can lead to the precipitation of calcium carbonate.

When hyperkalemia occurs in patients treated with digitalis, calcium should be administered for the same indications as in patients not treated with digitalis (eg, widening of the QRS complex or loss of P waves) even though hypercalcemia potentiates the cardiotoxic effects of digitalis. In such patients, a dilute solution can be administered slowly, infusing 10 mL of 10 percent calcium gluconate in 100 mL of 5 percent dextrose in water over 20 to 30 minutes, to avoid acute hypercalcemia [1]. In patients with hyperkalemia due to digitalis toxicity, the administration of digoxin-specific antibody fragments is the preferred therapy. (See "Digitalis (cardiac glycoside) poisoning", section on 'Electrolyte abnormalities'.)

Insulin with glucose — Insulin administration lowers the serum potassium concentration by driving potassium into the cells, primarily by enhancing the activity of the Na-K-ATPase pump in skeletal muscle [1,5]. Glucose is usually given with insulin to prevent the development of hypoglycemia. However, insulin should be given alone if the serum glucose is ≥250 mg/dL (13.9 mmol/L) [6]. The serum glucose should be measured every hour for five to six hours after the administration of insulin, given the risk of hypoglycemia.

One commonly used regimen for administering insulin and glucose is 10 to 20 units of regular insulin in 500 mL of 10 percent dextrose, given intravenously over 60 minutes. Another regimen consists of a bolus injection of 10 units of regular insulin, followed immediately by 50 mL of 50 percent dextrose (25 g of glucose). This regimen may provide a greater early reduction in serum potassium since the potassium-lowering effect is greater at the higher insulin concentrations attained with bolus therapy. However, hypoglycemia occurs in up to 75 percent of patients treated with the bolus regimen, typically approximately one hour after the infusion [7]. To avoid this complication, we recommend subsequent infusion of 10 percent dextrose at 50 to 75 mL/hour and close monitoring of blood glucose levels every hour for five to six hours.

The administration of glucose without insulin is **not** recommended, since the release of endogenous insulin can be variable and the attained insulin levels are generally lower with a glucose infusion alone [8]. Furthermore, in susceptible patients (primarily diabetic patients with hyporeninemic hypoaldosteronism), hypertonic glucose in the absence of insulin may acutely increase the serum potassium concentration by raising the plasma osmolality, which promotes water and potassium movement out of the cells [9-11].

The effect of insulin begins in 10 to 20 minutes, peaks at 30 to 60 minutes, and lasts for four to six hours [7,12-14]. In almost all patients, the serum potassium concentration drops by 0.5 to 1.2 mEq/L [14-17]. In particular, although patients with renal failure are resistant to the glucose-lowering effect of insulin, they are not resistant to the hypokalemic effect, because Na-K-ATPase activity is still enhanced [18,19]. (See "Carbohydrate and insulin metabolism in chronic kidney disease".)

Repeated dosing — Removal of excess potassium from the body (eg, with hemodialysis or a gastrointestinal cation exchanger) is sometimes not feasible or must be delayed. Such patients can be treated with either a continuous infusion of insulin and glucose or bolus infusions of insulin with glucose, repeated every two to four hours, with serial monitoring of blood glucose levels.

Remove potassium from the body — The effective modalities described above only transiently lower the serum potassium concentration. Thus, additional therapy is typically required to remove excess potassium from the body, except in patients who have reversible hyperkalemia resulting from increased potassium release from cells due, for example, to metabolic acidosis or insulin deficiency and hyperglycemia. (See "Causes and evaluation of hyperkalemia in adults", section on 'Increased potassium release from cells'.)

The three available modalities for potassium removal are diuretics, gastrointestinal cation exchangers (eg, patiromer, sodium polystyrene sulfonate [SPS], and zirconium cyclosilicate [ZS-9]), and dialysis. In patients with a hyperkalemic emergency, diuretics should **not** be the only method used to remove potassium from the body.

Loop diuretics in patients without severe renal impairment — Loop diuretics increase potassium loss in the urine in patients with normal or mild to moderately impaired renal function, particularly when combined with saline hydration to maintain distal sodium delivery and flow. However, patients with persistent hyperkalemia typically have impaired renal potassium secretion, and there are no data demonstrating a clinically important short-term kaliuretic response to diuretic therapy. Thus, diuretics should **not** be used as the only means to remove potassium from the body in patients with a hyperkalemic emergency.

In hypervolemic patients with preserved renal function (eg, patients with heart failure), we administer 40 mg of intravenous furosemide every 12 hours or a continuous furosemide infusion. In euvolemic or hypovolemic patients with preserved renal function, we administer isotonic saline at a rate that is appropriate to replete hypovolemia and maintain euvolemia, followed by 40 mg of intravenous furosemide every 12 hours or a continuous furosemide infusion.

If renal function is not preserved, we use a combination of an intravenous isotonic bicarbonate or isotonic saline infusion plus intravenous furosemide at doses that are appropriate for the patient's renal function. (See "Loop diuretics: Maximum effective dose and major side effects".)

Dialysis and gastrointestinal cation exchangers — Gastrointestinal cation exchangers, including patiromer, ZS-9, and SPS, bind potassium in the gastrointestinal tract in exchange for other cations, such as sodium or calcium. Such therapies can be used to treat hyperkalemia in patients with or without severe renal impairment.

Hemodialysis in patients with severe renal dysfunction — Hemodialysis is indicated in hyperkalemic patients with severe renal impairment, and is preferable to cation exchangers if the patient has functioning vascular access for dialysis and if the procedure can be performed without delay. However, if hemodialysis cannot be performed promptly (eg, within six hours), we administer gastrointestinal cation exchange therapy (preferably **not** SPS) and then perform hemodialysis as soon as possible.

Patiromer or ZS-9 — When using a cation exchanger in patients with a hyperkalemic emergency, we use patiromer if it is available (8.4 g, repeated daily as needed), rather than SPS. ZS-9 is not yet approved for use in hyperkalemic patients. Although both patiromer and ZS-9 (which is not yet available) may have a role in acutely reducing serum potassium in patients with hyperkalemic emergency, this has yet to be established. Our approach is based upon short-term effects of this drug in a separate patient population (ie, those treated for chronic moderate hyperkalemia). (See 'Patiromer' below.)

SPS in rare settings — SPS may also lower the serum potassium in patients presenting with a hyperkalemic emergency [20,21]. In one retrospective uncontrolled study, for example, 501 patients with acute hyperkalemia were treated with 15 to 60 g of SPS; serum potassium decreased by a mean of 0.93 mEq/L by the time the serum potassium was measured again (typically within 24 hours) [21]. However, adverse effects were common and two patients developed bowel necrosis, a well-described complication of SPS [22-26].

SPS with or without sorbitol should **not** be given to the following patients because they may be at high risk for intestinal necrosis [23,24,27,28]:

- Postoperative patients
- Patients with an ileus or who are receiving opiates
- Patients with a large or small bowel obstruction
- Patients with underlying bowel disease, eg, ulcerative colitis or Clostridium difficile colitis

Even if restoration of renal function or dialysis is not possible or immediately available, SPS should **not** be given in these high-risk settings; if other cation exchangers are not available, such patients can be managed with repeated doses of insulin and glucose (or continuous infusions) until dialysis can be performed. Other measures include the administration of isotonic bicarbonate and high-dose diuretics (if there is residual urine output). (See 'Sodium bicarbonate' below.)

Thus, we suggest that SPS be used (in conjunction with the rapidly acting transient therapies mentioned above) **only** in a patient who meets **all** of the following criteria:

- Patient has potentially life-threatening hyperkalemia
- Dialysis is not readily available
- Newer cation exchangers (eg, patiromer) are not available
- Other therapies to remove potassium (eg, diuretics, rapid restoration of kidney function) have failed or are not possible

In addition, if SPS is used, other orally administered drugs should be taken at least three hours before or three hours after the dose of SPS [29]. SPS binds to and prevents the absorption of many common medications.

The majority of intestinal necrosis cases associated with SPS occurred when the resin was administered with sorbitol [22-26]. In addition, intestinal necrosis was induced in a rat model by sorbitol alone or by sorbitol mixed with SPS but not with SPS alone [25]. Thus, it was presumed that sorbitol was required for the intestinal injury. As a result, the US Food and Drug Association (FDA) issued a recommendation in September 2009 that SPS should **no longer be administered in sorbitol** [22]. Despite this, many hospitals and pharmacies only stock sodium polystyrene sulfonate premixed in sorbitol. SPS alone is not always available and, when available, comes as a powder that must be reconstituted.

However, the association of SPS in sorbitol with intestinal necrosis may be coincidental since sorbitol is so widely used in conjunction with SPS. In addition, contemporary studies have found that SPS alone can cause intestinal necrosis in rats and have suggested that the previously noted toxicity of sorbitol alone in rats may have resulted from the hypertonic solution in which it was suspended [30].

Multiple clinical cases of intestinal necrosis with SPS and similar cation exchange resins without sorbitol have been reported [31-34]. In addition, intestinal necrosis has been reported in patients receiving SPS in a reduced concentration (33 percent) of sorbitol [22]. Thus, intestinal necrosis appears to be a complication of SPS independent of sorbitol.

When given, SPS with or without sorbitol can be administered orally, and SPS without sorbitol can be administered as a retention enema. Oral dosing is probably more effective if intestinal motility is not impaired. The oral dose is usually 15 to 30 g, which can be repeated every four to six hours as necessary. Single doses are probably less effective [35].

When given as an enema, 50 g of SPS is mixed with 150 mL of tap water (**not** sorbitol). After cleansing enema with tap water at body temperature, the resin emulsion should be administered at body temperature through a rubber tube placed at approximately 20 cm from the rectum with the tip well into the sigmoid colon. The emulsion should be introduced by gravity and flushed with an additional 50 to 100 mL of non-sodium-containing fluid. The emulsion should be kept in the colon for at least 30 to 60 minutes and, preferably, two to four hours, followed by a cleansing enema (250 to 1000 mL of tap water at body temperature) [36]. The enema can be repeated every two to four hours, as necessary.

Despite modest efficacy and the risk of catastrophic consequences, SPS remains the most widely used treatment for hyperkalemia [22,37]. In a six-month single-center survey from an emergency department, 1001 patients received SPS in sorbitol, while only 188 received other therapies [37].

Other therapies — Beta-2-adrenergic agonists (eg, inhaled albuterol) and intravenous sodium bicarbonate have been studied as potential rapidly acting therapies to reduce the serum potassium in hyperkalemic patients. Although they can be used in addition to calcium, insulin (with glucose), and potassium removal therapy, they should **not** be used in place of these treatments.

Beta-2-adrenergic agonists — Given the potential adverse effects described below, the authors and reviewers of this topic believe that intravenous epinephrine should **not** be used in the treatment of hyperkalemia. Albuterol is not frequently used but can be considered as transient therapy in patients who have symptoms or serious ECG manifestations of hyperkalemia despite therapy with calcium and insulin with glucose, or in patients in whom dialysis is not appropriate or not feasible.

Like insulin, the beta-2-adrenergic agonists drive potassium into the cells by increasing the activity of the Na-K-ATPase pump in skeletal muscle [1,38]. Beta-2-adrenergic receptors in

skeletal muscle also activate the inwardly directed Na-K-2Cl cotransporter, which may account for as much as one-third of the uptake response to catecholamines [39].

Beta-2-adrenergic agonists can be effective in the acute treatment of hyperkalemia, lowering the serum potassium concentration by 0.5 to 1.5 mEq/L [7,8,16,40,41]. Albuterol, which is relatively selective for the beta-2-adrenergic receptors, can be given as 10 to 20 mg in 4 mL of saline by nebulization over 10 minutes (which is 4 to 8 times the dose used for bronchodilation). Alternatively and where available, albuterol 0.5 mg can be administered by intravenous infusion. In patients who cannot tolerate nebulized albuterol, and if intravenous therapy is not available, subcutaneous terbutaline is a potential alternative [41]. The peak effect is seen within 30 minutes with intravenous infusion and at 90 minutes with nebulization [40].

Albuterol and insulin with glucose have an additive effect, reducing serum potassium concentration by approximately 1.2 to 1.5 mEq/L [7,14,42]. Thus, although albuterol should not be used as monotherapy in hyperkalemic patients with end-stage renal disease (ESRD), it can be added to insulin plus glucose to maximize the reduction in serum potassium [7]. One problem in patients on maintenance hemodialysis is that lowering the serum potassium concentration by driving potassium into the cells can diminish subsequent potassium removal during the dialysis session (from 50 to 29 mEq in one report), possibly leading to rebound hyperkalemia after dialysis [43].

Potential side effects of the beta-2 agonists include mild tachycardia and the possible induction of angina in susceptible subjects. Thus, these agents should probably be avoided in patients with active coronary disease. In addition, all patients with ESRD should be monitored carefully since they may have subclinical or overt coronary disease. (See "Risk factors and epidemiology of coronary heart disease in end-stage renal disease (dialysis)".)

Sodium bicarbonate — Raising the systemic pH with sodium bicarbonate results in hydrogen ion release from the cells as part of the buffering reaction. This change is accompanied by potassium movement into the cells to maintain electroneutrality. The use of bicarbonate for the treatment of hyperkalemia was mainly based upon small uncontrolled clinical studies [44-46]. However, in a study that compared different potassium-lowering modalities in 10 patients undergoing maintenance hemodialysis, a bicarbonate infusion (isotonic or hypertonic) for up to 60 minutes had no effect on the serum potassium concentration [16]. This lack of benefit was confirmed in several subsequent studies of hemodialysis patients [47-49].

Given the limited efficacy, we do **not** recommend the administration of sodium bicarbonate as the **only** therapy for the acute management of hyperkalemia, even in patients with mild to moderate metabolic acidosis [16,47-49]. However, prolonged bicarbonate therapy appears to be beneficial in patients with metabolic acidosis, particularly when administered as an isotonic infusion rather than bolus ampules of hypertonic sodium bicarbonate [16]. In one series, for example, the administration of isotonic sodium bicarbonate in a constant infusion to patients with a baseline serum bicarbonate of 18 mEq/L had little effect at one and two hours but significantly lowered the serum

potassium from 6 mEq/L at baseline to 5.4 and 5.3 mEq/L at four and six hours, respectively; the serum bicarbonate increased to 28 mEq/L at one hour and 30 mEq/L at six hours [48].

In addition, acute or chronic bicarbonate (alkali) therapy may be warranted to treat acidemia independent of hyperkalemia [45]. (See "Approach to the adult with metabolic acidosis", section on 'Overview of therapy' and "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease".)

When bicarbonate is given in the acute setting, we recommend the administration of an isotonic solution (eg, 150 mEq in 1 L of 5 percent dextrose in water over two to four hours), assuming the patient can tolerate the volume load. There is a potential hazard of giving hypertonic solutions, such as the standard ampule of 50 mEq of sodium bicarbonate in 50 mL. In addition, multiple doses can lead to hypernatremia [16].

Over the long term, in patients with chronic kidney disease (CKD), there are a variety of benefits from treating metabolic acidosis, and alkali therapy is recommended to maintain a near-normal serum bicarbonate, independent of any effect on the serum potassium concentration. (See "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease", section on 'Treatment of metabolic acidosis in CKD'.)

PATIENTS WITHOUT A HYPERKALEMIC EMERGENCY — Identifying patients who do **not** have a hyperkalemic emergency is presented above. (See 'Determining the urgency of therapy' above.)

Patients who do not have a hyperkalemic emergency can generally be divided into two groups (algorithm 1) (see 'Determining the urgency of therapy' above):

- Those who, despite needing to have their potassium lowered promptly, do not require rapidly acting therapy with calcium and insulin with glucose. Such patients with severe renal impairment are typically treated with dialysis (preferably hemodialysis) with or without the use of a gastrointestinal cation exchanger (eg, patiromer). In patients with normal renal function or mild to moderate renal impairment, correcting the cause of hyperkalemia (eg, drugs, hypovolemia) will generally suffice, in addition to treatment with saline infusion and loop diuretics.
- Those who can safely have their serum potassium lowered slowly. Such patients can usually be treated with therapies that gradually reduce the serum potassium, such as a low-potassium diet, loop or thiazide diuretics, or a reduction or cessation of medicines that can increase the serum potassium. With the introduction of patiromer and zirconium cyclosilicate (ZS-9), it is anticipated that gastrointestinal cation exchangers will be utilized more frequently in these patients for chronic control of the serum potassium.

Patients who need prompt serum potassium reduction — Identifying patients who should have their serum potassium promptly lowered but who do not require rapidly acting

therapy (ie, calcium and insulin with glucose), is presented above. (See 'Determining the urgency of therapy' above.)

Those with severe renal impairment — In patients with severe renal impairment who need prompt serum potassium reduction, dialysis should be performed right away if it is logistically feasible (ie, regular working hours, availability of staff, and presence of a suitable vascular access). If prompt dialysis is not logistically feasible, then a gastrointestinal cation exchanger (preferably patiromer or ZS-9, if and when available) can be used to remove potassium from the body until such time that dialysis can be performed.
(See 'Gastrointestinal cation exchangers' below.)

Dialysis — Dialysis is indicated in hyperkalemic patients with severe renal impairment. Hemodialysis is preferred since the rate of potassium removal is many times faster than with peritoneal dialysis [50]. Hemodialysis can remove 25 to 50 mEq of potassium per hour, with variability based upon the initial serum potassium concentration, the type and surface area of the dialyzer used, the blood flow rate, the dialysate flow rate, the duration of dialysis, the potassium concentration of the dialysate, and the patient's muscle mass [1,12].

One of the major determinants of the rate of potassium removal is the potassium gradient between the plasma and dialysate. Issues related to the removal of potassium with hemodialysis and potential adverse effects are discussed in detail separately. (See "Acute hemodialysis prescription".)

A rebound increase in serum potassium concentration occurs after hemodialysis in all patients in whom potassium is removed since the reduction in serum potassium during dialysis creates a gradient for potassium movement out of the cells. The magnitude of this effect was evaluated in a study of 14 stable maintenance hemodialysis patients [51]. The average serum potassium concentrations at baseline, during hemodialysis, and up to six hours after hemodialysis were 5.7, 3.6, and 5 mEq/L, respectively. Thus, the serum potassium concentration should usually not be measured soon after the completion of hemodialysis, since the results are likely to be misleading.

The postdialysis rebound after hemodialysis is more pronounced in patients undergoing acute hemodialysis for hyperkalemia due to massive release of potassium from injured cells (eg, tumor lysis, rhabdomyolysis) and after regular maintenance hemodialysis in patients with a high predialysis serum potassium concentration [51].

Rapidly acting transient therapies given before dialysis, such as insulin with glucose or albuterol, have a twofold effect: Total potassium removal is reduced due to lowering of the serum potassium concentration [43,52]; and the potassium rebound is greater because of the wearing off of the effect of the transient therapies. The potassium rebound is also increased with a high-sodium dialysate since the increase in plasma osmolality creates a gradient for water and then potassium efflux from the cells [53].

Patients who have a large postdialysis rebound may require daily dialysis or continuous renal replacement therapy to avoid recurrent severe hyperkalemia.

Those without severe renal impairment — Patients who have moderate hyperkalemia and either normal renal function or mild to moderate renal impairment can usually be managed without dialysis. Treatment of such patients typically includes a gastrointestinal cation exchanger in addition to reversing the cause of hyperkalemia. As an example, a patient with moderate chronic kidney disease (CKD) treated with a renin-angiotensin-aldosterone system (RAAS) inhibitor who presents with a serum potassium of 6.0 mEq/L may be treated with a cation exchanger (such as patiromer), temporary discontinuation of the RAAS inhibitor, as well as other therapies that are appropriate for the clinical setting (ie, bicarbonate therapy if the patient has metabolic acidosis, and diuretic therapy if the patient is hypervolemic).

Patients who can have the serum potassium lowered slowly — Identifying patients who do not need prompt lowering of the serum potassium and can be safely treated with therapy that gradually lowers the serum potassium is presented above. (See 'Determining the urgency of therapy' above.)

In addition to correcting reversible causes of hyperkalemia, our approach in such patients is as follows:

- All such patients should receive dietary counseling to reduce potassium intake (table 5). (See "Patient education: Low-potassium diet (The Basics)" and "Patient education: Low-potassium diet (Beyond the Basics)" and 'Dietary modification' below.)
- In addition, thiazide or loop diuretics can be used in patients who have hypertension or hypervolemia. (See 'Diuretics' below.)
- Patients who continue to have moderate hyperkalemia despite dietary modification and diuretics can be treated chronically with newer gastrointestinal cation exchangers (eg, patiromer). (See 'Gastrointestinal cation exchangers' below.)

Dietary modification — It is rare for hyperkalemia to occur exclusively due to excessive intake, although such cases have been described [54,55]. By contrast, the presence of renal disease predisposes to hyperkalemia in patients consuming potassium [56]. In addition to renal impairment, other predisposing factors include hypoaldosteronism and drugs that inhibit the RAAS can result in significant hyperkalemia after only modest intake of potassium. Such patients should be assessed for their intake of potassium-rich foods (refer to https://www.kidney.org/atoz/content/potassium), and counseled to avoid these foods (table 6). Other, occult sources of excessive potassium include salt substitutes [57,58], various forms of pica [59], and "alternative" nutritional therapies [60,61]. Often, the adoption of a potassium-restricted diet (refer to https://www.kidney.org/atoz/content/potassium) normalizes serum potassium levels and affords the resumption of RAAS antagonists (table 7), even in patients with CKD.

Diuretics — Loop and thiazide diuretics increase potassium loss in the urine in patients with normal or mild to moderately impaired renal function, particularly when combined with saline hydration to maintain distal sodium delivery and flow. However, patients with

persistent hyperkalemia typically have impaired renal potassium secretion, and there are no data demonstrating a clinically important short-term kaliuretic response to diuretic therapy.

Although data are limited, chronic diuretic therapy is probably effective over the long term by increasing urinary potassium excretion, particularly in patients with mild to moderate CKD [62]. For patients with moderate hyperkalemia whose renal function is not severely impaired, we suggest a trial of diuretics if otherwise appropriate (eg, hypertension or hypervolemia). Among patients with hyperkalemia due to angiotensin inhibitors, many can be controlled with a low-potassium diet and diuretic therapy.

Gastrointestinal cation exchangers — Patiromer and ZS-9 are nonabsorbable compounds that exchange calcium or sodium and hydrogen, respectively. We do **not** use sodium polystyrene sulfonate (a cation exchange resin) as chronic therapy for such patients.

Patiromer — Patiromer is a spherical, nonabsorbable organic polymer, formulated as a powder for suspension, which binds potassium in the colon in exchange for calcium [63,64].

In a phase II, open-label dose-finding trial (AMETHYST-DN), 306 diabetic patients with an estimated glomerular filtration rate (eGFR) of 15 to 59 mL/min/1.73 m^2 and either mild or moderate hyperkalemia (serum potassium of 5.1 to 5.5, or 5.6 to 5.9 mEq/L, respectively) were randomly assigned to a range of initial patiromer doses (4.2 g twice daily to 16.8 g twice daily) [65]; follow-up was 52 weeks. All patients were also treated with stable doses of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), or both, often in combination with spironolactone. At four weeks, the change in serum potassium from baseline ranged from -0.35 to -0.55 mEq/L with initial doses of 4.2 g twice daily to 12.6 g twice daily among those with mild hyperkalemia, and from -0.87 to -0.97 mEq/L with initial doses of 8.4 g twice daily to 12.6 g twice daily among those with moderate hyperkalemia. Approximately one-third of patients had a single adjustment (up or down) to their patiromer dose; most required no adjustment. At 52 weeks, serum potassium concentrations remained in the normal range with continued patiromer therapy. Discontinuation of patiromer resulted in an increase in the serum potassium within three days.

There were no treatment-related serious adverse events in AMETHYST-DN. The most common treatment-related side effects included constipation (6.3 percent of patients) and hypomagnesemia (8.6 percent of patients). Hypomagnesemia occurred more commonly with higher doses of patiromer (16.7 percent among those assigned 33.6 g/day compared with 5.4 percent among those assigned 8.4 g/day). Severe hypomagnesemia (a serum magnesium <1.2 mg/dL) developed in 13 patients (4.3 percent).

The OPAL-HK study extended these observations in a phase III, randomized placebo-controlled trial in outpatients with CKD and hyperkalemia [66]. In OPAL-HK, 243 patients with an eGFR of 15 to 59 mL/min/1.73 m^2 and a serum potassium of 5.1 to 6.4 mEq/L on two occasions while receiving a stable dose of an ACE inhibitor or ARB received either 4.2 or 8.4 g of patiromer twice daily for four weeks, depending upon whether their serum

potassium was below or above 5.5 mEq/L. The mean decrease in serum potassium at four weeks was 1.0 mEq/L (0.6 and 1.2 mEq/L with lower and higher doses, respectively); approximately 75 percent of patients achieved the target serum potassium of 3.8 to 5.0 mEq/L. The decline in serum potassium was steepest during the first three days.

The 107 patients whose baseline serum potassium was 5.5 mEq/L or greater and who achieved the target serum potassium during the initial four-week treatment period were randomly assigned to patiromer or placebo for another eight weeks. Serum potassium remained the same in patients continuing patiromer and increased by 0.7 mEq/L in those assigned to placebo. The incidence of hyperkalemia (5.5 mEq/L or greater) was significantly higher in the placebo group (60 versus 15 percent). Serious adverse events were rare and not likely to be related to treatment; constipation was the most common side effect, occurring in 11 percent of patients during the initial four-week period. As with the AMETHYST-DN trial, hypomagnesemia developed in some patients (eight patients [3 percent] developed magnesium levels <1.4 mg/dL).

There are several limitations of the OPAL-HK and AMETHYST-DN trials. The effect of patiromer in patients with acute hyperkalemia or end-stage renal disease (ESRD) was not evaluated. In addition, patients in these trials were not routinely prescribed a low-potassium diet, only one-half of patients in the OPAL-HK trial were receiving loop or thiazide diuretics, and the number of patients in the AMETHYST-DN trial who received diuretics was not reported. Both a low-potassium diet and the use of loop or thiazide diuretics can be long-term strategies to prevent hyperkalemia in many patients with CKD who are treated with ACE inhibitors or ARBs. (See 'Diuretics' above.)

In addition to binding cations, patiromer can bind other drugs in the gastrointestinal tract. Clinically important interactions with ciprofloxacin, thyroxine, and metformin have been identified; these three drugs need to be administered more than three hours before or after patiromer [67].

Zirconium cyclosilicate — Sodium zirconium cyclosilicate (ZS-9) is an inorganic, nonabsorbable crystalline compound that exchanges both sodium and hydrogen ions for potassium throughout its intestinal transit [63]. The efficacy of ZS-9 in hyperkalemic outpatients was evaluated in two nearly identical phase III, randomized placebo-controlled trials:

- In the Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) study, 258 adult patients with persistent hyperkalemia (serum potassium that is greater than or equal to 5.1 mEq/L) entered a 48-hour open-label run-in during which they received 10 g of ZS-9 three times daily; 69 percent had CKD (although patients with ESRD were excluded), 70 percent were taking a renin-angiotensin system inhibitor, and the majority had heart failure, diabetes mellitus, or both [68]. Of the 258 patients who entered the open-label run-in, 237 (92 percent) achieved a normal serum potassium (3.5 to 5.0 mEq/L) at 48 hours and were then randomly assigned to placebo or 5 g, 10 g, or 15 g of ZS-9 once daily for four weeks. During randomized therapy, the mean serum potassium was significantly lower with

ZS-9 (4.8, 4.5, and 4.4 mEq/L with 5, 10, and 15 g dosing, respectively) as compared with placebo (5.1 mEq/L). Similarly, the proportion of normokalemic patients at the end of the study was significantly greater with ZS-9 (71 to 85 percent as compared with 48 percent with placebo). Serious adverse events were uncommon and were not significantly increased with ZS-9. However, edema was more common with the 10 g and 15 g doses compared with placebo (6 and 14 versus 2 percent), as was hypokalemia (10 and 11 versus 0 percent). Among a subgroup of 87 patients with heart failure, edema occurred in eight (15 percent) of those receiving ZS-9 and in one (4 percent) receiving placebo [69]. It is unclear whether or not higher edema rates with ZS-9 are due to an increased sodium load (which, as noted above, would be expected since ZS-9 exchanges sodium for potassium).

- In another trial, 753 adult patients with a serum potassium of 5.0 to 6.5 mEq/L were randomly assigned to receive 1.25, 2.5, 5, or 10 g of ZS-9 three times daily for 48 hours; 74 percent had CKD (patients with ESRD were excluded), 67 percent were receiving a renin-angiotensin system inhibitor, and most patients had diabetes, heart failure, or both [70]. A normal serum potassium (3.5 to 4.9 mEq/L) at 48 hours was attained by 543 patients (72 percent), and these individuals were then reassigned to receive placebo or 1.25, 2.5, 5, or 10 g of ZS-9 once daily for two weeks. The serum potassium at two weeks was significantly lower in patients receiving 5 and 10 g doses of ZS-9 as compared with placebo (by approximately 0.3 and 0.5 mEq/L, respectively) but not with 1.25 and 2.5 g doses. Adverse events were similar with placebo and ZS-9.

In these trials, the steepest decline in serum potassium with ZS-9 occurred during the first four hours of therapy [68,70]. This suggests an acute effect on intestinal potassium secretion, rather than simply a reduction in potassium absorption. Neither trial evaluated the long-term efficacy and safety of ZS-9, and neither studied patients with acute hyperkalemia or ESRD.

Do not use SPS or other resins — The most widely used cation exchange resin has been sodium polystyrene sulfonate (SPS). Although "SPS" is often used as an abbreviation for sodium polystyrene sulfonate, SPS is actually a brand name for sodium polystyrene sulfonate in sorbitol.

Cation exchange resins do not appear to be more effective in removing potassium from the body than laxative therapy. Although uncommon, cation exchange resins can produce severe side effects, particularly intestinal necrosis, which may be fatal. (See 'SPS in rare settings' above.)

Given these concerns, SPS or other resins should **not** be used in patients with chronic mild or moderate hyperkalemia who do not have a hyperkalemic emergency and who do not require a prompt reduction in serum potassium. (See 'Determining the urgency of therapy' above.)

DRUG-INDUCED HYPERKALEMIA — A variety of drugs can raise the serum potassium, primarily by interfering with the renin-angiotensin-aldosterone system. Probably the most

common are angiotensin inhibitors (eg, angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARBs]), aldosterone antagonists and other potassium sparing diuretics (eg, spironolactone, eplerenone, and amiloride), digitalis, and nonsteroidal anti-inflammatory drugs (table 3). (See "Causes and evaluation of hyperkalemia in adults", section on 'Reduced aldosterone secretion'.)

These drugs should be discontinued, or the dose reduced at least temporarily, until the hyperkalemia is controlled.

PREVENTION — There are several measures that can help to prevent hyperkalemia in patients with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD). In addition to a low-potassium diet, the following modalities have been effective in stable maintenance hemodialysis patients (see "Patient education: Low-potassium diet (Beyond the Basics)"):

- Avoid episodes of fasting, which can increase potassium movement out of the cells due, at least in part, to reduced insulin secretion [8,71]. In a study of 10 stable patients on maintenance hemodialysis who did not have diabetes mellitus, fasting for 18 hours led to a mean 0.6 mEq/L rise in the serum potassium concentration, which was completely prevented when the protocol was repeated with the administration of low-dose insulin with dextrose [71]. Thus, nondiabetic patients with ESRD who are undergoing elective surgery should, if they are in the hospital, receive parenteral glucose-containing solutions when fasting overnight.
- Avoid, if possible, drugs that raise the serum potassium concentration in patients with a serum potassium ≥5.5 mEq/L. These include inhibitors of the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), direct renin inhibitors, aldosterone antagonists, and nonselective beta blockers (eg, propranolol and labetalol) [72,73]. Beta-1-selective blockers such as metoprolol and atenolol are much less likely to cause hyperkalemia [8,74]. (See "Causes and evaluation of hyperkalemia in adults", section on 'Beta blockers'.)

Patients with CKD or heart failure are often treated with RAAS inhibitors. A variety of preventive measures can diminish the risk of hyperkalemia [72]. These include:

- Close monitoring of the serum potassium concentration and estimated glomerular filtration rate (eGFR), particularly after changes in RAAS inhibitor therapy.
- Dietary restriction of potassium. (See "Patient education: Low-potassium diet (Beyond the Basics)".)
- Avoidance or discontinuation of other drugs that impair potassium excretion (eg, nonsteroidal anti-inflammatory drugs).
- The utilization of low initial doses and evidence-based final doses of RAAS inhibitors for specific indications (eg, heart failure, proteinuric CKD). The dose should be reduced with moderate hyperkalemia (serum potassium of ≤5.5 mEq/L) and therapy should be

discontinued if the serum potassium rises above 5.5 mEq/L unless the serum potassium can be reduced by diuretic therapy.

- The use of thiazide or loop diuretics whenever otherwise indicated.
- There are no good data on the chronic efficacy of oral alkali therapy (sodium bicarbonate or sodium citrate) for the treatment of persistent hyperkalemia. Most such patients have CKD with or without hypoaldosteronism. There are a variety of benefits from treating metabolic acidosis in such patients, and alkali therapy is typically recommended, independent of any effect on the serum potassium concentration. (See "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease", section on 'Treatment of metabolic acidosis in CKD'.)

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Hyperkalemia (The Basics)" and "Patient education: Low-potassium diet (The Basics)")
- Beyond the Basics topic (see "Patient education: Low-potassium diet (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The urgency of treatment of hyperkalemia varies with the presence or absence of the symptoms and signs associated with hyperkalemia, the severity of the potassium elevation, and the cause of hyperkalemia. Our approach to therapeutic urgency is as follows (algorithm 1) (see 'Determining the urgency of therapy' above):
  - Hyperkalemic emergency − Patients who have clinical signs or symptoms of hyperkalemia (eg, muscle weakness or paralysis, cardiac conduction abnormalities, cardiac arrhythmias), patients with severe hyperkalemia (serum potassium >6.5 mEq/L), and patients with moderate hyperkalemia (serum potassium >5.5 mEq/L) plus significant renal impairment and ongoing tissue breakdown or potassium absorption) have a hyperkalemic emergency.

- Patients needing prompt therapy − Some patients with moderate hyperkalemia but without a hyperkalemic emergency should, nonetheless, have their potassium lowered promptly (ie, within 6 to 12 hours). Such patients include hemodialysis patients who present outside of regular dialysis hours, patients with marginal renal function and/ormarginal urine output, or hyperkalemic patients who need to be optimized for surgery.
- Patients who can have the potassium lowered slowly − Most patients with hyperkalemia have chronic, mild (≤5.5 mEq/L) or moderate (5.5 to 6.5 mEq/L) elevations in serum potassium due to chronic kidney disease (CKD) or the use of medications that inhibit the renin-angiotensin-aldosterone system ([RAAS] or both). Such patients do not require urgent lowering of the serum potassium.

● Patients with a hyperkalemic emergency should receive (table 1) (see 'Patients with a hyperkalemic emergency' above):

- Intravenous calcium to antagonize the membrane actions of hyperkalemia. (See 'Calcium' above.)
- Intravenous insulin (typically given with intravenous glucose) to drive extracellular potassium into cells. (See 'Insulin with glucose' above.)
- Therapy to rapidly remove excess potassium from the body (ie, loop or thiazide diuretics if renal function is not severely impaired, a gastrointestinal cation exchanger, and/ordialysis [preferably hemodialysis] if renal function is severely impaired). (See 'Remove potassium from the body' above.)
- Treatment of reversible causes of hyperkalemia, such as correcting hypovolemia and discontinuing drugs that increase the serum potassium (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], inhibitors of the RAAS). (See "Causes and evaluation of hyperkalemia in adults" and 'Drug-induced hyperkalemia' above.)
- Continuous cardiac monitoring and serial electrocardiograms (ECGs). The serum potassium should be measured at one to two hours after the initiation of treatment. The timing of further measurements is determined by the serum potassium concentration and the response to therapy. Patients who receive insulin, with or without dextrose, should undergo hourly glucose measurements for up to six hours in order to monitor for hypoglycemia. (See 'Monitoring' above.)

● Treatment of patients who do not have a hyperkalemic emergency generally depends upon how promptly the serum potassium should be lowered (algorithm 1) (see 'Patients without a hyperkalemic emergency' above):

- Patients needing prompt potassium lowering are typically treated with hemodialysis (if they have severe renal dysfunction) with or without the use of a gastrointestinal cation exchanger (eg, patiromer). In patients with normal renal function or mild to moderate renal impairment, correcting the cause of hyperkalemia (eg, drugs, hypovolemia) will generally suffice, in addition to treatment with saline infusion and loop diuretics; a gastrointestinal cation exchanger is sometimes used in such patients. (See 'Patients who need prompt serum potassium reduction' above.)

- Patients who can safely have their serum potassium lowered slowly are usually treated with therapies that gradually reduce the serum potassium, such as a low-potassium diet, loop or thiazide diuretics, or a reduction or cessation of medicines that can increase the serum potassium. With the introduction of patiromer and ZS-9, it is anticipated that gastrointestinal cation exchangers will be utilized more frequently in these patients for chronic control of the serum potassium. (See 'Patients who can have the serum potassium lowered slowly' above.)

● There are several measures that can help to prevent hyperkalemia or worsening of hyperkalemia in patients with CKD, particularly those with end-stage renal disease (ESRD). In addition to a low-potassium diet, the following modalities have been effective in stable maintenance hemodialysis patients (see 'Prevention' above and "Patient education: Low-potassium diet (Beyond the Basics)"):

- Avoid episodes of fasting, which can increase potassium movement out of the cells due, at least in part, to reduced insulin secretion.
- In patients with moderate hyperkalemia, avoid, if possible, drugs that raise the serum potassium concentration. These include RAAS inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), direct renin inhibitors, aldosterone antagonists, and nonselective beta blockers (eg, propranololand labetalol) (table 3).
- Avoidance or discontinuation of other drugs that impair potassium excretion (eg, NSAIDs).
- The use of thiazide or loop diuretics whenever otherwise indicated.

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