Article

Pathophysiology, Evaluation, and Treatment of Hyperkalemia

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Learning Objectives

1. To summarize the mechanisms underlying internal and external potassium balance
2. To define the pathophysiology of hyperkalemia
3. To summarize current approaches to acute and chronic hyperkalemia

Introduction

Potassium is the predominant cation inside of cells, and it plays essential roles, especially in setting the resting potential of most cells throughout the body. Potassium homeostasis requires coordination of external balance, derived primarily via gastrointestinal absorption and renal excretion, and internal balance, meaning the asymmetric distribution of K^+ between the intracellular space and the extracellular space. This article briefly reviews aspects of normal internal and external potassium balance and then discusses the pathophysiology of hyperkalemia.

Cardiovascular Outcomes and Mortality

Population-based studies have consistently demonstrated a strong correlation between dietary potassium intake and poor cardiovascular outcomes. In most analyses, the mortality risk related to plasma potassium concentration is U shaped, with excess in both the hypokalemic and hyperkalemic ranges (1). A 2018 meta-analysis of the CKD Prognosis Consortium included patient-level data from 27 international cohorts (10 general population, 10 with CKD, 7 high cardiovascular risk) (1). At 6.9 years, the lowest all-cause mortality risk was associated with potassium 4 to 4.5 mEq/L. Compared with potassium of 4.2 mEq/L, the associated hazard ratio was 1.22 (95% CI, 1.15 to 1.29) for potassium 5.5 mEq/L and 1.49 (95% CI, 1.26 to 1.76) for potassium 3.0 mEq/L. There were similar U-shaped associations for cardiovascular mortality and ESKD.

Total Body Potassium Distribution

Total body potassium abundance has been estimated to be about 55 mmol/kg, or between 3000 and 4000 mmol for a 70-kg person, with approximately 98% of the cation found intracellularly. Most of the intracellular potassium resides in skeletal muscle, given the abundance of this tissue in the body, although significant amounts are also in other tissues, including red blood cells and liver. Only approximately 2% of the total body potassium, or 70 mmol, exists in the extracellular compartment, and precise control of the distribution between intracellular and extracellular compartments is imperative to ensure proper cell function, particularly for electrically excitable cells such as cardiac and skeletal muscle and neurons. This distribution is maintained by a system that ultimately requires activity of the Na^+/K^+ adenosine triphosphate (ATP)ase, which uses energy to actively pump potassium into cells against its electrochemical gradient. The tendency of potassium to lead out of cells, via membrane channels, leads most cells to have a membrane voltage oriented with the cell interior negative, relative to the cell exterior. Disruption of this system can result in pathologic aberrations in plasma potassium and secondarily affect cell membrane potential, which increases the risk of life-threatening cardiac arrhythmias.

Regulation of Potassium Homeostasis

Daily dietary potassium intake generally ranges between 50 and 150 mmol, which is roughly equivalent to the entire extracellular pool. Avoiding significant and sustained aberrations in both total and plasma potassium levels requires a quick and efficient system to maintain homeostasis. The potassium homeostatic mechanism involves coordinated regulation between its major components, including the gastrointestinal tract, which absorbs dietary potassium; skeletal muscle, which harbors the majority of intracellular potassium and is involved in intracellular/extracellular redistribution; and the kidney, which is the predominant site of potassium excretion, most of which derives from secretion along the aldosterone-sensitive distal nephron (ASDN). Coordination of these components is accomplished via hormonal control, including contributions from aldosterone, insulin, adrenergic stimuli, and plasma potassium itself.

Gastrointestinal Absorption

Dietary potassium intake can vary widely across populations as well as temporally in a given individual. In general, potassium consumed in the diet is well absorbed.

Renal Potassium Reabsorption and Secretion

Proximal Tubule. Potassium is freely filtered by the glomerulus and then reabsorbed along the proximal tubule (PT), where approximately 60%–65% of total reabsorption occurs. Reabsorption occurs primarily via a paracellular pathway wherein potassium flux occurs secondary to bulk water reabsorption.

Thick Ascending Limb of Henle. Approximately 20%–25% of the filtered potassium load is reabsorbed along the thick ascending limb of Henle (TAL). The reabsorptive pathway along this segment depends on apical activity of the sodium-potassium-2 chloride cotransporter (NKCC2). The renal outer medullary potassium channel (ROMK or Kir1.1) is expressed and active along the apical plasma membrane of the TAL and permits a portion of the potassium that traverses the NKCC2 to recycle across the apical membrane; coupled with basolateral chloride efflux, via ClC chloride channels, this generates a net-positive lumen potential. This positive potential then drives paracellular potassium reabsorption along with other cations, such as Ca^{2+} and Mg^{2+}. When this mechanism fails, as in Bartter syndrome or during furosemide administration, patients present with hypokalemia caused by renal potassium losses. Although potassium is reabsorbed along the TAL under most conditions, recent experiments show that the transport direction may reverse when animals consume a low-sodium/high-potassium diet, in which case the TAL becomes a potassium-secreting segment (2). Under these conditions, furosemide administration becomes potassium sparing. Whether similar effects occur is humans has not been studied.

Distal Convoluted Tubule. Studies have failed to consistently demonstrate meaningful quantities of potassium reabsorption or secretion along the distal convoluted tubule (DCT). The contribution of this segment is, however, integral to maintaining potassium balance—a finding highlighted by dysregulated potassium homeostasis in Mendelian tubulopathies affecting the DCT such as Gitelman syndrome and familial hyperkalemic hypertension (also called pseudohypoaldosteronism type 2 or Gordon syndrome). Substantial work over the past decade has demonstrated that this segment's role in potassium reabsorption is a consequence of its ability to act as a modulator of sodium flow to the more distal connecting segment and collecting duct (CD), major sites of sodium-dependent potassium secretion. Inasmuch as these more distal segments require sodium reabsorption to generate a lumen-negative transepithelial voltage to secrete potassium, the DCT can increase or decrease potassium excretion by allowing more or less sodium to flow distally. The DCT accomplishes this by modulating apical sodium reabsorption via the sodium-chloride cotransporter, which is regulated by a molecular signaling pathway (WNK-SPAK) that is known to be potassium sensitive and allows this system to sense and respond to aberrations in plasma potassium levels (3,4). (See "Integrated renal potassium excretion: The potassium switch" below for additional details.)

Connecting Tubule and Collecting Duct. The connecting tubule (CNT) and the CD are targets of aldosterone and act as the predominant sites for active potassium secretion in the body. After reabsorption along the PT and TAL, approximately 10% of the filtered potassium load reaches the CNT. Along the CNT and CD, net potassium transport can range from nearly complete reabsorption of the remaining filtered load (approximately 10%) to net secretion. Under normal conditions, potassium secretion predominates and is responsible for the majority of potassium excreted in the urine. This system relies on a net negative lumen potential created by apical sodium reabsorption via the epithelial sodium channel (ENaC) to drive electrogenic potassium secretion via apically expressed ROMK and BK (Maxi K) channels. Extensive work has clearly shown that this system is activated by aldosterone via mineralocorticoid receptor signaling (5,6), which is why this nephron segment is often referred to as the aldosterone-sensitive distal nephron (ASDN).

The secretory capacity of these segments is exceptional, with animal models demonstrating minimal changes in plasma potassium levels after the consumption of heavily potassium-loaded diets ($\leq$5% wt/wt). It has become clear that under typical dietary conditions, the CNT is the most active potassium secretory site, whereas the CD typically becomes active primarily when aldosterone secretion is stimulated by depletion of the extracellular fluid volume or by hyperkalemia (7).

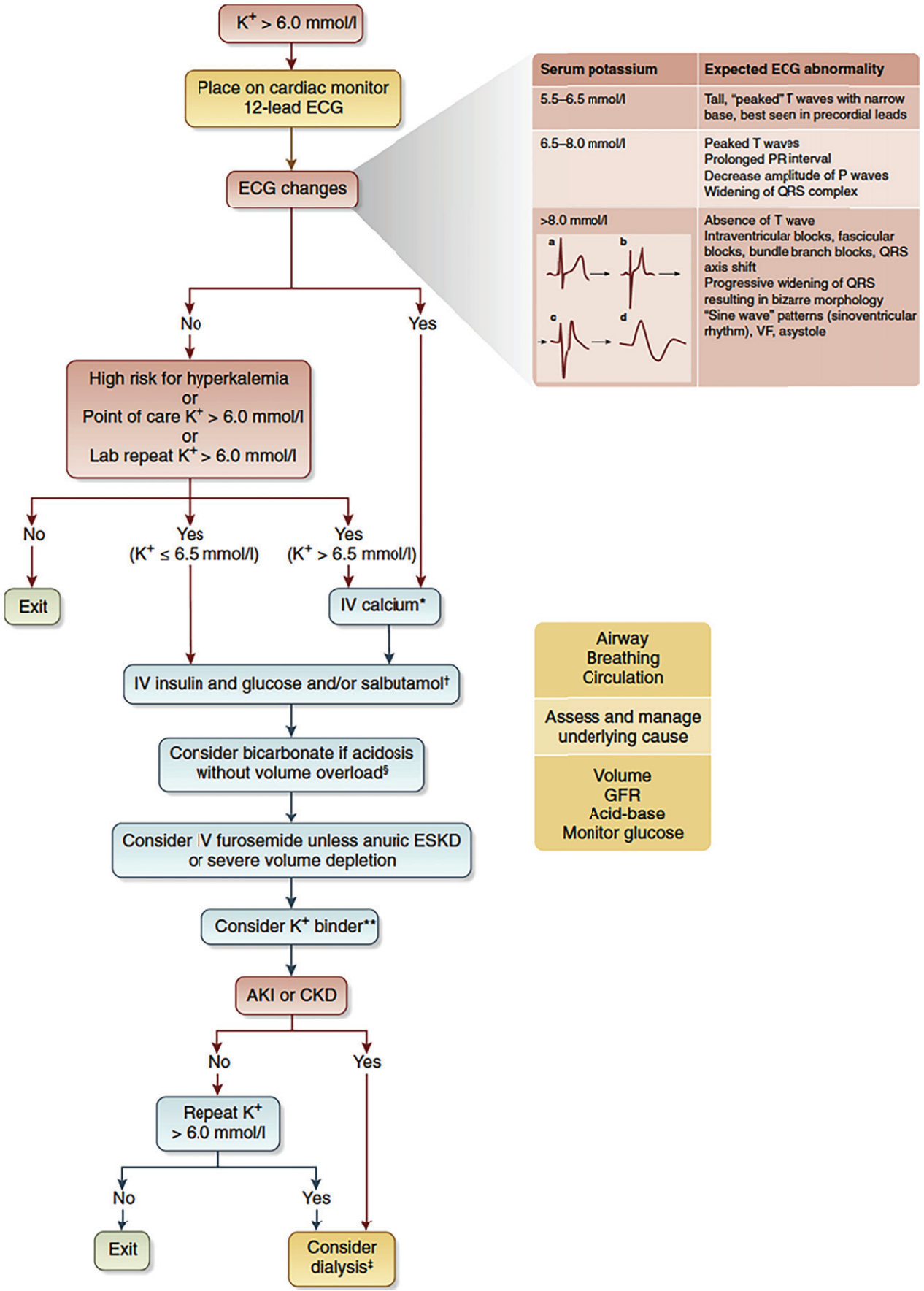
During states of potassium depletion, potassium can be reabsorbed along this segment; α-intercalated cells are the major cells responsible for potassium reabsorption. They express the hydrogen-potassium ATPase (H^+-K^+ ATPase), for which two isoforms exist: HKa_1 and HKa_2. In models of experimental hypokalemia, H^+-K^+ ATPase abundance increases (8) to maximally conserve total body potassium.

Integrated Renal Potassium Excretion: The Potassium Switch

During the past several years, an increased understanding of renal potassium handling has emerged, in large part driven by the molecular solutions to monogenic diseases of potassium retention and potassium wasting. Gitelman syndrome, an autosomal recessive disease, typically presents with profound hypokalemia (see the NephSAP article on hypokalemia) and is caused by mutations in the gene encoding NCC, expressed exclusively along the DCT (9). Yet, as noted above, this segment of the nephron does not transport substantial amounts of potassium, which suggests that the mechanisms of potassium wasting are indirect.

The mirror image disease, familial hyperkalemic hypertension (also known as pseudohypoaldosteronism type 2 or Gordon syndrome) is a monogenic disease characterized by hyperkalemia, which can be severe (10). Yet, once again, we now know that the mutations that cause the disease do so primarily by activating NCC, again having effects primarily along the DCT, which does not transport potassium.

The resolution to this apparent paradox is the potassium switch (Figure 2), which links the DCT with the ASDN (primarily CNT and CD) and aldosterone. Work has made clear that a dominant factor modulating NCC is the plasma potassium concentration; when plasma potassium concentration is high, NCC is "turned off" (dephosphorylated). When the plasma potassium concentration is low, NCC is "turned on" (4). Hyperkalemia therefore both stimulates aldosterone secretion by the adrenal glands AND inhibits NCC. This means that more sodium flows into a nephron segment (the CNT/CD) that is primed to secrete potassium by aldosterone. The converse situation is also relevant. When plasma potassium is low, NCC is activated. This limits sodium delivery to the ASDN, thereby limiting potassium secretion and therefore potassium excretion. These monogenic diseases (Gitelman syndrome and familial hyperkalemic hypertension) cause abnormalities in plasma potassium concentration because they break this switch (11).


K+ > 6.0 mmol/l
Place on cardiac monitor 12-lead ECG
ECG changes
No
Yes
High risk for hyperkalemia or Point of care K+ > 6.0 mmol/l or Lab repeat K+ > 6.0 mmol/l
No
Yes (K+ ≤ 6.5 mmol/l)
Yes (K+ > 6.5 mmol/l)
Exit
IV calcium*
IV insulin and glucose and/or salbutamol†
Consider bicarbonate if acidosis without volume overload§
Consider IV furosemide unless anuric ESKD or severe volume depletion
Consider K+ binder**
AKI or CKD
No
Yes
Repeat K+ > 6.0 mmol/l
No
Yes
Exit
Consider dialysis‡
Serum potassium
Expected ECG abnormality
5.5–6.5 mmol/l
Tall, "peaked" T waves with narrow base, best seen in precordial leads
6.5–8.0 mmol/l
Peaked T waves
Prolonged PR interval
Decrease amplitude of P waves
Widening of QRS complex
>8.0 mmol/l
a
b
c
d
Absence of T wave
Intraventricular blocks, fascicular blocks, bundle branch blocks, QRS axis shift
Progressive widening of QRS resulting in bizarre morphology
"Sine wave" patterns (sinoventricular rhythm), VF, asystole
Airway
Breathing
Circulation
Assess and manage underlying cause
Volume
GFR
Acid-base
Monitor glucose

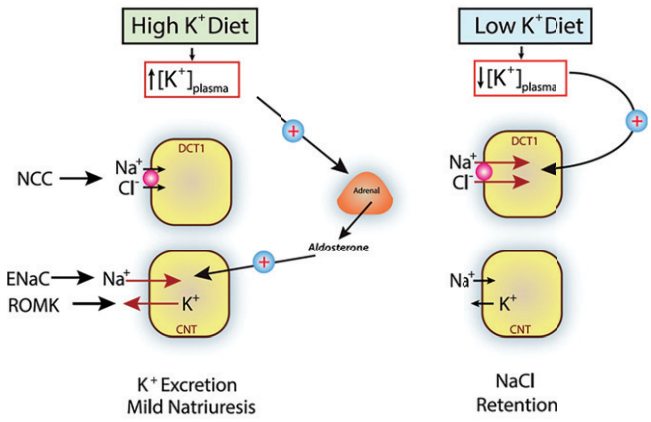


Figure 2. Potassium switch. The 'potassium switch' involves the potassium-induced interaction between the distal convoluted tubule (DCT) and the connecting tubule (CNT). When dietary K^+ intake is high (left panels), elevated plasma potassium stimulates aldosterone secretion. As the NCC is turned off by high K^+, sodium delivery to the activated CNT is high and sodium exchange for potassium is robust. In contrast, when dietary K^+ intake is low, NCC is stimulated directly, but aldosterone secretion is inhibited. Most sodium is therefore reabsorbed electroneutrally along the DCT, preventing potassium loss. Used with permission from reference 11 (Ellison DH, Terker AS, Gamba G: Potassium and its discontents: new insight, new treatments. *J Am Soc Nephrol* 27: 981–989, 2016).

The signaling pathway that underlies the potassium switch has also been clarified by monogenic diseases. NCC is activated by phosphorylation along its amino terminal cytoplasmic domain (12). The kinase that is primarily responsible is SPAK, which is expressed broadly along the distal nephron (13). SPAK itself is activated when it is phosphorylated. In this case, the kinase responsible is primarily WNK4, produced by one of the genes that, when mutated, leads to hyperkalemic hypertension (14). The WNK kinases are sensitive to intracellular chloride concentration (15), which turns out to be the link with plasma potassium. When plasma potassium is high, it increases intracellular chloride concentration secondarily, which turns off WNK kinases (4,16). Conversely, when the plasma potassium concentration is low, that reduces intracellular chloride concentration, leaving WNKs in a chloride-unbound state, which activates them.

The potassium switch discovery appears to resolve the "aldosterone paradox," the observation that the same hormone, aldosterone, can mediate primarily kaliuresis when induced by hyperkalemia, and primarily sodium retention, when induced primarily by angiotensin II (via extracellular volume depletion) (17). We can now see that during hyperkalemia, aldosterone concentrations are high, activating the epithelial sodium channel along the CNT/CD, generating a lumen-negative voltage. Yet, NCC is turned off, meaning that there is little salt reabsorption along the DCT. In this situation, Na flows distally, leading to robust potassium secretion, but sites of sodium reabsorption are mostly shifted from more proximal (DCT) to more distal (CNT/CD); net sodium reabsorption is not stimulated.

By contrast, when extracellular fluid volume is low, angiotensin II is stimulated. In this case, NCC is activated by angiotensin II, while at the same time, aldosterone activates the CNT/CD. In this case, sodium delivery to the CNT/CD is low, and therefore, even though the segment is activated, transport there is limited, limiting potassium secretion. In contrast, because sodium reabsorption is stimulated all along the distal nephron, net sodium retention occurs.

Diagnosis and Evaluation

Although flame photometry ushered in the era of electrolyte measurement in the 1940s, nearly all laboratories now determine potassium concentration using ion-sensitive electrodes. Three different methods of collection are currently used to estimate the concentration of extracellular potassium in plasma, serum, or whole blood. Each approach has strengths and limitations, and all three are used clinically.

Serum is collected into tubes that often have red tops and contain a clotting activator, like silica. The collected blood is allowed to clot at rest, and then potassium is measured in the clear serum component. When blood clots, a certain amount of potassium is released from red cells; this is *in vitro* hemolysis and should be distinguished from hemolysis related to phlebotomy or *in vivo* hemolysis, resulting from disease. Additionally, some potassium is released from platelets and leukocytess. These processes account for the fact that serum potassium concentrations typically exceed plasma or whole blood measurements by 0.1–0.7 mM (18). Spectrophotometric measurement of hemolysis is typically used to detect hemolysis when serum

Figure 1. Algorithm for treating moderate or severe hyperkalemia in adults. *IV 1 g calcium gluconate (10 ml of 10% solution [repeated up to 3 times, if necessary after 5 minutes], each containing 93 mg elemental calcium, 2.3 mmol) or calcium chloride (10 ml of 10% solution, 273 mg elemental calcium, 6.8 mmol). †IV regular insulin 5 units plus 25 g glucose (50 ml of 50%) is as effective as albuterol (salbutamol) 10 mg nebulized; insulin and albuterol may have an additive effect. Beware of hypoglycemia. IV bicarbonate (1 amp of 50 ml of 8.4% solution, Na 50 mmol, HCO_3 50 mmol) over 15 minutes. **Potassium binders: sodium polystyrene sulphonate 15–60 g orally/rectally (do not give with sorbitol) or zirconium cyclosilicate 10 g 3/d (patiromer not advisable because onset of action is 7 hours). This guidance is suggestive because there are limited data on onset of action with no head-to-head studies between potassium binders. ‡Hemodialysis is the modality of preference. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Used with permission from reference 18 (Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, Kovesdy CP, Kline GA, Lindner G, Obrador GT, Palmer BF, Cheung M, Wheeler DC, Winkelmayer WC, Pecoits-Filho R; Conference Participants: Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int* 97: 42–61). License (CC BY NC ND).

measurements are performed in laboratories, with a recommended threshold of <2%, but higher values are common, especially when blood is obtained from intravenous catheters (19).

The other approaches to determine the amount of potassium in circulating blood use plasma and whole blood. Plasma is collected into heparinized tubes and obtained by centrifugation; the potassium concentration is obtained with an ion-sensitive electrode autoanalyzer. By contrast, whole blood techniques measure potassium immediately after the sample is obtained, without further processing; these methods determine potassium concentrations that are essentially those in plasma and are used commonly in emergency departments and intensive care units. Patients who have substantial leukocytosis ($>50\times10^9$/L) (20) or thrombocytosis are at risk for pseudohyperkalemia, when serum measurements are used.

In fact, determination of whole blood potassium is used increasingly, owing to its speed and accessibility. It is often argued that serum potassium is the criterion standard, inasmuch as the American Society of Clinical Pathology has the most clearly developed quality control metrics for its use. In many recent trials, whole blood methods have been used routinely (21). In many series, it has been noted that the value obtained from whole blood point-of-care testing is often 0.3–0.5 mM lower than that obtained from serum in the laboratory (22). Overall, these data raise the possibility that whole blood potassium is a more accurate measure of the relevant physiologic variable than is serum (23).

In the acute setting, an important goal of treating hyperkalemia is to prevent arrhythmias. Unfortunately, arrhythmias are not closely correlated with serum or blood potassium concentrations. Several well-described electrocardiographic (ECG) changes occur in the setting of hyperkalemia, including tall "peaked" T waves, a prolonged P-R interval, intraventricular blocks, widening of the QRS complexes, eventually resulting in "sine wave" patterns, ventricular fibrillation, and asystole. Some work has suggested that ECG changes are reliable and predictive of more serious arrhythmias (24), but the associated findings have not included such early signs as peaked T waves.

An interesting approach explored recently has used artificial intelligence and deep learning algorithms to detect subtle ECG changes that are associated with hyperkalemia. Such approaches have been termed bloodless blood tests and have used ECG leads in the dialysis unit (25,26). Recently, approaches using routine ECGs have also been shown to correlate well with the results of serum potassium measurements and to exceed the performance of experienced cardiologists at detecting hyperkalemia (27,28). In one study a deep learning model was trained to detect potassium >5.5 mEq/L using >1.5 million ECGs from 449,380 patients and tested in a validation cohort including 61,965 CKD patients (28). The area under the receiver operating curve ranged from 0.853 to 0.883. Using a high sensitivity operating point to maximize its utility as a screening tool, the negative predictive value was >99%. This is as good as, or better than, many other commonly used screening tools, including mammography and colonoscopy for detecting breast cancer and colorectal cancers, respectively.

Of course, the utility of such approaches currently is limited because of the ease of measuring blood potassium concentrations clinically and the lack of implemented software. On the other hand, were these approaches able to predict serious arrhythmias more accurately than humans examining ECG tracings, they could become very useful in emergency settings.

Causes and Risk Factors

In approaching a patient with an elevated blood potassium concentration, the first question is whether the measurement reflects a true increase in circulating levels. Given that 95% of body potassium is inside of cells, and that methods for measurement depend on blood collection, it is not surprising that cell leakage can artificially elevate potassium; this phenomenon is called pseudohyperkalemia. Hemolysis during or after blood collection is the most common cause. A falsely elevated potassium level may occur with fist clenching during phlebotomy, mechanical trauma, tourniquet use >1 minute, and during blood clotting, but, as noted, most laboratories include spectrophotometric analysis of hemolysis and have cutoffs of 1%–2%. Additionally, patients with elevated leukocyte or platelet counts may have release from those formed elements. In general, if formed elements are increased (as discussed above), or if there is suspicion of hemolysis, the potassium should be assessed by use of the converse technique (serum versus whole blood or plasma). If there is uncertainty, treatment is often provided.

A second question to address is the duration of hyperkalemia. Causes that involve shifting of potassium from inside of cells are typically acute and do not involve a change in body potassium content. By contrast, chronic hyperkalemia, with or without a temporary increase, requires an impairment of potassium secretion along the ASDN. Most common cases of hyperkalemia, at least in patients who do not have ESKD, reflect a congruence of factors that impair renal potassium secretion. Although high potassium intake may contribute, its role may have been overemphasized in the past, and there has been a reconsideration of dietary recommendations for patients with CKD or other hyperkalemic risk factors (29). In view of the cardioprotective effects of diets high in potassium, especially those that emphasize fruits and vegetables, many authorities now advocate that patients at risk for hyperkalemia focus on eating a healthy diet, without undue focus on potassium restriction; this may help address the low adherence to typical CKD diets observed in practice (30).

It is not surprising that the major risk factors for hyperkalemia include kidney failure (acute or chronic), use of drugs that block the renin/angiotensin/aldosterone system (RAAS), and acidosis. Other common drug-induced causes are numerous, and they have been reviewed (31). Patients with ESKD are at special risk. On the basis of epidemiologic evidence, other frequently identified factors include male sex, lower body mass index, malignancy, and diabetes (32).

Whereas these risk factors increase the prior probability of true hyperkalemia, other important, but less common, bona fide causes of hyperkalemia exist. These include hyperkalemic periodic paralysis, an autosomal dominant disorder in which episodes of flaccid weakness and intermittent myotonia can be precipitated by cold, exercise, fasting, or the ingestion of small amounts of potassium. The most common abnormality in hyperkalemic periodic paralysis is a point mutation in the *SCNA4* gene for the α subunit of the skeletal muscle cell sodium channel (a channel that is molecularly distinct from ENaC in the kidney) (33).

Hypoaldosteronism can result from Addison disease or be isolated. Isolated hypoaldosteronism, often a part of hyporeninemic

hypoaldosteronism, was previously diagnosed commonly in patients with chronic diabetes or interstitial nephritis; it is often viewed as synonymous with type 4 renal tubular acidosis, but some cases of hyperkalemic acidosis have distal resistance to aldosterone, rather than aldosterone insufficiency, and have been termed hyperkalemic distal RTA (34)

Pseudohypoaldosteronism type 1 is usually diagnosed early in life and presents with severe salt wasting and hyperkalemia. It can result from genetically defective ENaC channels and can be inherited in an autosomal recessive manner or from mutations in the mineralocorticoid receptor itself, and either be inherited in an autosomal dominant manner or be *de novo* (35). The recessive form is sometimes referred to as systemic and presents with severe lifelong salt losing. The form resulting from mutations in the mineralocorticoid receptor is sometimes called the renal form and is milder; many times, salt supplementation becomes unnecessary by 1–3 years of age. Interestingly, the salt wasting is likely secondary to both a deficiency in ENaC and secondary inhibition of NCC resulting from hyperkalemia. Animal models have indicated that the salt wasting can be mitigated by correcting the plasma potassium, thereby reactivating NCC (36), and this phenomenon has recently been reported in humans (37). A third form of pseudohypoaldosteronism type 1 is acquired and is associated with urinary tract abnormalities and urinary infections (35).

Pseudohypoaldosteronism type 2, which is now also referred to as familial hyperkalemic hypertension or Gordon syndrome, also presents with hyperkalemia, but in this case is associated with normal BP (early in life) and hypertension later. It occurs most commonly as an autosomal dominant disease, but some cases, discussed below, can also be recessive. The disease is caused by mutations in genes encoding proteins that affect NCC. The first discovered were mutations in WNK (with no lysine) kinase 1 and *WNK4*, and they resulted in increased phosphorylation and activation of NCC (38). Inhibition of potassium channels may also be involved, but the phenotype is mimicked in mice that have activated NCC alone (39).

Mutations have more recently been identified in genes that modulate WNK activity, including Kelch-like 3 and Cullin 3 (40), which are detected more commonly. These proteins are part of the Cullin ring ligase complex, which leads to ubiquitylation of proteins, targeting them for degradation via the proteasome. The mutations appear to disrupt the ability of the complex to bind to WNK kinases, leading to their accumulation; the WNK kinase mutations are now known to disrupt their binding to *KLHL3*, preventing their degradation (41). Most mutations of Cullin 3 and *KLHL3* are inherited in a dominant manner, but some *KLHL3* mutations are recessive (Table 1).

- The sodium-chloride cotransporter (NCC) in the distal convoluted tubule modulates potassium excretion by regulating the amount of sodium delivered to the connecting segment and collecting duct.
- NCC is dephosphorylated (turned off) when the plasma potassium is high and phosphorylated (turned on) when the plasma potassium is low.

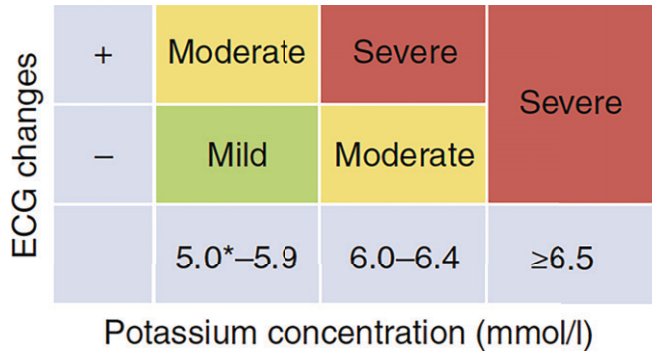


Figure 3. KDIGO-recommended classification of hyperkalemia. *indicates that hyperkalemia is defined as either >5.0 or >upper limit of normal potassium for the laboratory. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease. Used with permission from reference 18 (Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, Kovesdy CP, Kline GA, Lindner G, Obrador GT, Palmer BF, Cheung M, Wheeler DC, Winkelmayer WC, Pecoits-Filho R; Conference Participants: Potassium homeostasis and management of dyskalemia in kidney diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int* 97: 42–61). License (CC BY NC ND).

Prevention

Expert guidelines suggest that plasma potassium should be monitored within several weeks of starting or increasing drugs that block the RAAS (18).

Treatment

The decision to treat hyperkalemia, and the urgency of such treatment, is not standardized. One approach to this decision is to categorize hyperkalemia according to a consensus-based algorithm that incorporates both measured potassium and ECG changes and that classifies hyperkalemia as mild, moderate, and severe (Figure 3). The indications for controlling hyperkalemia in the long term are discussed below.

Acute Hyperkalemia

A KDIGO controversies conference recently addressed the management of hyperkalemia (18). The initial management of acute hyperkalemia typically includes the use of insulin/glucose and β agonists for potassium >6.5 mEq/L, with use of intravenous calcium if EKG changes are present; the algorithm also recommends calcium use if a repeat serum or blood potassium is above 6.5 mEq/L, even in the absence of ECG changes. Bicarbonate may be considered if acidosis is present. Intravenous loop diuretics and potassium binders are also considered. Immediate short-term treatment of potentially

Table 1. Causes of pseudohyoaldosteronism

Type	Mode of Inheritance	Gene Mutations	Clinical Features
Pseudohypoaldosteronism type IA	Dominant	Mineralocorticoid receptor	Milder
Pseudohypoaldosteronism type IB	Recessive	Epithelial sodium channel	Severe phenotype
Pseudohypoaldosteronis type IIA	Dominant	WNK 1, WNK4, KLHL3, CUL 3	Hypertension, short stature, responsive to thiazides

Reprinted with permission from reference 34 (Batlle, D, Arruda, J: Hyperkalemic forms of renal tubular acidosis: clinical and pathophysiological aspects. *Adv Chronic Kidney Dis* 28: 321–333, 2018).

life-threatening hyperkalemia is based on experience and opinion; although it is relatively standardized (42), wide variation in approaches persists (43) (Figure 1).

Stabilize the Membrane. For urgent cases, calcium is usually administered; calcium chloride contains three times the amount of calcium as calcium gluconate, but the gluconate salt is sometimes, although not always, preferred as it causes less local irritation. The European Resuscitation Council recommends use of 10 ml 10% calcium chloride over 2–5 minutes in hyperkalemic patients with ECG changes (44); the KDIGO conference recommended calcium gluconate, but this would require 30 ml of a 10% solution to obtain the same amount of elemental calcium (18). The effects are short lived (30-60 minutes) and doses can be repeated if ECG changes persist. Hyperkalemia depolarizes the resting potential of myocytes, putting it closer to the threshold potential, increasing the likelihood of aberrant action potentials. Calcium raises the threshold potential, thereby restoring the difference between it and the resting potential; calcium may have other effects on cardiomyocytes, as well.

Shift Potassium into Cells. Insulin shifts potassium into cells primarily by stimulating the Na/K ATPase, is clearly effective in lowering potassium concentrations, and forms the centerpiece of most approaches to acute hyperkalemia; it is usually given with glucose to avoid hypoglycemia, unless the baseline serum glucose exceeds 250 mg/dL. The insulin effect occurs quickly (10-20 minutes) and can last four to six hours. The most recent guidelines from the UK Renal Association are very clear and recommend that all patients with moderate or severe hyperkalemia (potassium >6 mEq/L) receive 10 units of insulin in 25 grams of glucose. When the baseline serum glucose is less than 126 mg/dl, this should be followed by 10% glucose at 50 ml/h for 5 hours, with a target glucose of 72-126 mg/dl) (https://renal.org/health-professionals/guidelines/guidelines-commentaries).

Yet, even using this approach, hypoglycemia may occur. A recent meta-analysis evaluated retrospective cohort studies of lower dose strategies with low or moderate risk of bias (45). The standard approach was considered to be 10 units of insulin and the alternative approaches included 5 units, 0.1 units/kg, and <10 units. Alternative dosing had lower pooled odds of hypoglycemia and severe hypoglycemia, without detected differences in potassium reduction.

β-Adrenergic agonists, primarily albuterol (also called salbutamol), can also be used to shift potassium into cells. The drug lowers plasma potassium by approximately the same amount as insulin, and its use by nebulizer is generally preferred over intravenous administration (42). Its effects have been reported to be additive with insulin, although studies have been small (46). A randomized control trial comparing nebulized albuterol and insulin with glucose, versus both treatments combined, is currently in progress (47).

Sodium bicarbonate has been used, but its effects are limited, and it has generally fallen out of favor unless there is systemic metabolic acidosis. The minimal effect of bicarbonate has been confirmed in several studies (48), although it should be noted that sustained alkali treatment in CKD has several other benefits and may enhance urinary potassium excretion in the long term.

Remove Potassium from the Body. Except when hyperkalemia is the result of an internal shift, removal from the body is the definitive approach. For individuals with kidney function, diuretic-induced kaliuresis is often effective. Although it is often stated that there is little experimental support for the use of diuretics to treat hyperkalemia in the short term, and there certainly are no large controlled studies of loop diuretic efficacy in this situation, many smaller physiologically based trials show preserved kaliuresis in situations of low GFR, as long as urine volumes increase (49,50). Therefore, in the absence of extracellular fluid volume depletion, loop diuretics should be given; using natriuretic (often higher) doses is essential because potassium clearance correlates with sodium clearance during loop diuretic administration (51).

When there is doubt about the utility of diuresis, or if forced diuresis fails, dialysis is often used. Hemodialysis is the most effective approach to rapid potassium removal, with rates of removal inversely proportional to dialysate potassium concentration (52). Each hemodialysis session removes approximately 70–100 mmol of potassium (53) The serum potassium concentration typically falls by 1 mmol/L during the first hour of dialysis, when the gradient between the serum and dialysate K^+ is highest, then by 1 mmol/L over the next 2 hours. It reaches a steady state during the last hour of the treatment.

Hemodialysis patients have a high risk of hyperkalemia, which is associated with mortality and may be responsible for 3%–5% of deaths (54). At the same time, there is also speculation that the sudden reduction in serum potassium that occurs during dialytic removal may be just as important (55). The most common time for hyperkalemic events in hemodialysis patients is immediately after the 3-day weekend break (56). The long interdialytic break also correlates with hospitalization (57) and mortality in hemodialysis patients (58). In a large study of 52,734 hemodialysis patients receiving three-times-weekly dialysis who underwent 533,889 repeated serum potassium measurements over a 2-year period, the

serum was >5.5 mEq/L in 20% of all measurements, particularly after the long interdialytic interval (*i.e.*, 24%, 16%, and 20% of measurements conducted on Monday, Wednesday, and Friday, respectively) (59).

In rigorous analyses, the investigators found that increasingly higher serum potassium levels were associated with incrementally higher short-term hospitalization risk. Serum potassium levels of 5.5–6.0 mEq/L obtained on Friday were potently associated with higher hospitalization risk within 4 days of measurement (adjusted odds ratio, 1.68; 95% CI, 1.22 to 2.30), whereas levels obtained on Monday and Wednesday were linked with mild to no greater risk, respectively. Notably, serum potassium levels >6.0 mEq/L were associated with greater hospitalization costs across all days of measurement. On the basis of data such as these, the UK Renal Association Clinical Practice Guideline on Haemodialysis recommends an optimal predialysis serum K^+ in the range of 4.0–6.0 mmol/L.

Although dialysate potassium concentrations <2 mM remove more potassium than those ≥2 mM , low dialysate potassium concentrations (0 or 1 mM) associate with mortality, at least when used in the long term—an association that is magnified in patients with higher predialysis potassium concentrations (60). Whether this association reflects confounding by indication is not clear, but very low dialysate potassium concentrations should typically be avoided, especially if ECG monitoring is not used.

Continuous renal replacement therapy (CRRT) is commonly used to treat critically ill patients, many of whom have hyperkalemia. Inasmuch as blood flow is lower in CRRT than in hemodialysis, potassium clearance is typically less, and therefore hemodialysis is preferred as first-line treatment. Nevertheless, there are individuals in whom hemodynamic considerations suggest the use of CRRT; in such patients, blood flow and replacement fluid/dialysis flow rates should be maximized initially; if persistent hyperkalemia is a problem, it may signal persistent tissue breakdown/ischemia (61).

Gastrointestinal Potassium Removal. Sodium polystyrene sulfonate (SPS), still often used with sorbitol, has been a common treatment for hyperkalemia, but its history is checkered. Even an initial report found little effect on plasma potassium concentration beyond that of sorbitol alone (62). Meaney et al. (63) found three clinical studies of its use, which reported lowering of approximately 1 mM within 1–3 days. Reports of serious gastrointestinal complications, especially when SPS was administered with sorbitol, caused the U.S. Food and Drug Administration (FDA) to recommend discontinuation of its use with sorbitol, but even when it is used without, intestinal necrosis may occur (64). SPS, however, is still administered with sorbitol in many settings. The FDA also recommends that SPS administration be separated temporally from that of other drugs because it can alter drug absorption. Given that there are now safer and clearly effective potassium-binding agents, many authorities recommend against using SPS (64); its price may be lower than the prices of the new agents, perhaps fostering continued use.

Two newer potassium-binding agents have been approved in the past 10 years: patiromer in 2015 and sodium zirconium cyclosilicate in 2018. Each has been shown to be effective in lowering plasma potassium, although neither has been compared directly with SPS in terms of efficacy. The sites of action, benefits, and side effects of each, as well as their physical chemistry, differ, although both lead to increased potassium removal through the gut.

In the setting of acute hyperkalemia, or during a transition from the acute phase of treatment to more sustained approaches, sodium zirconium cyclosilicate has the advantage of faster action, with potassium lowering beginning as early as 1 hour (11)—a result of its acting along both the small and the large intestines. Yet, a recent although somewhat limited study found little advantage to adding sodium zirconium cyclosilicate to standard treatment, including insulin and glucose (65). The UK Renal Association guidelines do provide sodium zirconium cyclosilicate (level 1B) and patiromer (level 1C) recommendations for treating acute hyperkalemia.

Chronic Hyperkalemia

There is no consensus regarding the optimal management of chronic hyperkalemia, although a common approach was recently summarized by KDIGO (18).

In the setting of chronic hyperkalemia, the focus has been on withdrawing offending drugs, increasing urinary excretion, increasing gastrointestinal removal, and possibly reducing intake (with the caveats noted above). Whereas reducing the doses of, or discontinuing, drugs that contribute to hyperkalemia has long been a core component of treatment, drugs that interfere with the RAAS are among the most effective in mitigating both cardiovascular and renal disease. Given the development of demonstrably safe and effective agents that can reduce plasma potassium, the possibility of combining RAAS inhibition with potassium-binding drugs is now being evaluated and is widely used.

Among the traditional approaches to mitigating hyperkalemia in patients taking RAAS blocking agents, and especially with CKD, is to increase urine sodium and water excretion with loop diuretics. Although lacking randomized controlled data, this approach is almost surely effective, as noted above, and inasmuch as potassium excretion can be normalized in patients with Addison disease, who lack aldosterone, as long as salt and water consumption provides sufficient distal flow. When such patients are hypertensive, as is often the case with CKD, loop diuretics can treat both the hyperkalemia and the hypertension.

Another traditional approach is to administer fludrocortisone. This mineralocorticoid agonist directly stimulates potassium secretion in the ASDN and can be quite effective. It also causes sodium retention, however, and directly counteracts many of the beneficial effects of RAAS blockers, making its use restricted to relatively rare cases of chronic hyperkalemia with salt wasting.

The development of new potassium-binding drugs has raised the prospect that preventive treatment with oral potassium-binding drugs might permit RAAS blockade to be continued in situations where it would otherwise require discontinuation. Unlike SPS, which has limited efficacy, poor tolerability, and potential safety issues, patiromer and sodium zirconium cyclosilicate are generally safe and well tolerated. There are now multiple studies showing their efficacy.

Patiromer was the first agent approved (Table 2) and is a powder for oral suspension. It is a cation exchange polymer that is not absorbed along the gastrointestinal tract, where it exchanges calcium for potassium, especially the colon. In one initial open-label trial, 306 diabetic patients with CKD (eGFR 15–59 ml/min per 1.73 m^2) and serum potassium of 5.1–5.9 mEq/L were randomized to

Table 2. Selected characteristics of K^+ binding agents for hyperkalemia

Characteristic	SPS	Patiromer	SZC
Approval date	1958	US, 2015; EU, 2017	US, 2018; EU, 2018
Mechanism of action	K^+ binding in exchange for Na^+ in GI tract (↑ fecal excretion)	K^+ binding in exchange for Ca^{2+} in GI tract (↑ fecal excretion)	K^+ binding in exchange for H^+ and Na^+ in GI tract (↑ fecal excretion)
Site of action	Colon	Colon	Small and large intestines
Selectivity for K^+	Nonselective; also binds Ca^{2+} and Mg^{2+}	Nonselective; also binds Na^+ and Mg^{2+}	Highly selective; also binds NH_4^+
Onset of action	Variable; several hours	7 h	1 h
Na^+ content	1500 mg per 15-mg dose	None	400 mg per 5-g dose
Ca^{2+} content	None	1.6 g per 8.4-g dose	None
Sorbitol content	20,000 mg per 15-g dose	4000 mg per 8.4-g dose	No sorbitol content
Dosing	15 g 1–4 times (oral); 30–50 g 1–2 times (rectal)	8.4 g QD (oral), titrate up to 16.8 g or 25.2 g QD	10 g TID (oral) for initial correction of hyperkalemia (for ≤48 h), then 5 g QOD to 15 g QD for maintenance
Serious AEs	Cases of fatal GI injury reported	None reported	None reported
Most common AEs	GI disorders (constipation, diarrhea, nausea, vomiting, gastric irritation), hypomagnesemia, hypokalemia, hypocalcemia, systemic alkalosis	GI disorders (abdominal discomfort, constipation, diarrhea, nausea, flatulence), hypomagnesemia	GI disorders (constipation, diarrhea, nausea, vomiting), mild to moderate edema

different doses of patiromer and followed up for 1 year. All patients were also treated with stable doses of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, or both, often in combination with spironolactone. Serum potassium decreased by −0.35 to −0.55 mEq/L at 4 weeks, with initial doses of 4.2–12.6 g twice daily among those with mild hyperkalemia, and from −0.87 to −0.97 mEq/L with initial doses of 8.4–12.6 g twice daily among those with moderate hyperkalemia. Serum potassium concentrations remained in the normal range at 1 year with continued patiromer therapy. Patiromer discontinuation resulted in an increase in the serum potassium within 3 days. There were no treatment-related serious adverse events in this trial, although constipation (6.3% of patients) and hypomagnesemia (8.6% of patients) was reported. Hypomagnesemia occurred more commonly with higher doses of patiromer (66).

In another early study of 237 patients with CKD who were receiving RAAS inhibitors and who had serum potassium levels of 5.1 to <6.5 mmol per liter, patiromer was given during a correction phase for 4 weeks followed by a randomized withdrawal phase. At week 4, 76% of the patients had reached the target potassium level (<5.1 mM). Subsequently, 107 patients were randomly assigned to patiromer (55 patients) or placebo (52 patients) for the randomized withdrawal phase. The median increase in the potassium level from baseline was greater with placebo than with patiromer ($P<0.001$); as in the other study, mild to moderate constipation was the most common adverse event (in 11% of the patients), and hypomagnesemia occurred (in 3%) (66).

An interesting recent study tested the effects of patiromer on serum and stool electrolytes in 27 anuric dialysis patients who had a tendency toward hyperkalemia at baseline. During 12 weeks, treatment with patiromer reduced serum potassium concentration (by 0.6 mM) and increased stool potassium excretion—effects that reversed when the treatment was discontinued. Additionally, during the treatment phase, serum calcium increased (from 8.9 to 9.1 mg/dL) and serum magnesium decreased (from 2.6 to 2.4 mg/dL) compared with pretreatment levels, and the changes in serum potassium and magnesium were directly related (67).

Patiromer has been shown to reduce plasma potassium concentrations for longer periods of time, in a variety of settings, and has permitted uptitration of RAAS-blocking drugs (68). The AMBER study was a phase 2 multicenter, randomized, double-blind, placebo-controlled study that was designed to determine whether concomitant use of patiromer would permit greater use of spironolactone for uncontrolled hypertension in participants with CKD (69). Participants were randomly assigned (1:1) to receive either placebo or patiromer (8.4 g once daily) in addition to open-label spironolactone (starting at 25 mg once daily). The primary endpoint was the between-group difference at week 12 in the proportion of patients taking spironolactone. Two hundred ninety-five patients were randomly assigned to spironolactone in addition to double-blind treatment with either placebo ($n=148$) or patiromer ($n=147$). At week 12, 66% of patients in the placebo group and 86% of patients in the patiromer group continued with spironolactone (statistically

significant). Adverse events were mostly mild or moderate in severity and occurred in 79 (53%) of 148 patients in the placebo group and 82 (56%) of 147 patients in the patiromer group. In a prespecified subgroup analysis of patients with heart failure, the treatment group was able to receive more spironolactone than the placebo group (70).

It appears that the approach of using potassium binders to permit continued RAAS blockade is being used commonly in a variety of healthcare settings. In one study, 288 veterans with hyperkalemia who were treated with patiromer were studied after patiromer initiation. All had heart failure, diabetes, or CKD, but not ESKD, and had a median age of 70 years. Potassium concentration reductions after patiromer initiation were, on average, −1.0 mM ($P<0.001$), and RAAS inhibitor therapy was continued in >80%–90% of patients (71).

A retrospective cohort study used data from a large dialysis provider and examined dialysis patients who had a medication order for patiromer or SPS or who had laboratory evidence of hyperkalemia. Patiromer initiators were 2.6 times more likely to have had multiple prior episodes of hyperkalemia. Sixty percent of patients' first patiromer orders remained open after 180 days, with statistically significant reductions in serum potassium, averaging approximately −0.5 mM.

In nearly all studies, the most common side effects of patiromer use are gastrointestinal intolerance, such as constipation, and hypomagnesemia, as mentioned above. Because the drug exchanges calcium for potassium, it does not deliver a sodium load, but it does alter divalent mineral metabolism. In addition to hypomagnesemia, some recent case reports have detected hypercalcemia in some patients (72).

Sodium zirconium cyclosilicate was approved in 2018 (Table 2). It is an insoluble, nonabsorbed cation exchange crystal that exchanges potassium for sodium. Zirconium silicates have been used extensively in medical and dental applications because of their safety; in the case of sodium zirconium cyclosilicate, the molecule is complexed with sodium. Many studies include a correction phase, often using higher doses, and then a maintenance phase at a lower, once-daily dose. Most do not use a placebo group during the initial correction phase, because leaving patients uncorrected might put them at risk. In one early study, treatment reduced serum potassium by 0.46 mM within 48 hours during the uncontrolled correction phase (73). After correction, patients were randomized to zirconium or placebo for 2 weeks, during which serum potassium concentration was lower in the treatment groups than in the placebo group.

Later studies have supported this efficacy and demonstrated more prolonged effects. In the HARMONIZE multisite randomized controlled study, 267 patients were treated during an open-label correction phase, followed up, and then randomized to 5 g or 10 g daily of sodium zirconium cyclosilicate in the controlled sustained phase. During the first 48 hours, serum potassium declined by 1.28 mmol/L. During the maintenance phase (days 8–29), serum potassium was 10% and 18% lower, with low and high sodium zirconium cyclosilicate doses, than with placebo ($P<0.001$ for both). More patients had normokalemia with sodium zirconium cyclosilicate 5 (58.6%) and 10 g (77.3%) versus placebo (24.0%), with the greatest number of normokalemic days in the 10-g group (74).

One group of patients at substantial risk of hyperkalemia is those with ESKD treated with dialysis. The DIALIZE study was a double-blind, placebo-controlled multicenter study in which patients with predialysis hyperkalemia were randomized to receive placebo or sodium zirconium cyclosilicate on nondialysis days over 4 weeks. One hundred ninety-six patients were randomized to sodium zirconium cyclosilicate or placebo. Significantly more patients in the treatment group (41.2%) maintained serum potassium concentrations below 5 mM than did patients treated with placebo (1.0%). Rescue therapy to reduce potassium was required in fewer patients receiving zirconium cyclosilicate compared with placebo (2.1% versus 5.1% respectively). There were no differences in adverse effects, and the weight gains in the two groups were similar (75).

The sodium load delivered with sodium zirconium cyclosilicate (Table 2) can be substantial and is believed to be the reason that sustained use has been associated with edema in >10% of patients, especially in those patients with eGFR <30 ml/min (76). This concern may be one factor leading many cardiologists to prefer patiromer to sodium zirconium cyclosilicate during sustained use (D.H. Ellison, unpublished observation). Otherwise, the drug is usually well tolerated, with constipation being the most commonly reported side effect.

One potential benefit of sodium zirconium cyclosilicate is that is also removes hydrogen ions and can increase the serum bicarbonate concentration (77). Acidosis complicating CKD is recognized increasingly as having adverse consequences, and a modest improvement in acid-base balance is likely to be beneficial (78). Roger et al. (77) examined data from three placebo-controlled phase 3 trials of sodium zirconium cyclosilicate. The results showed a significant dose-dependent increase in mean serum bicarbonate of 0.3 to 1.5 mM within 48 h of treatment. These changes were maintained over 29 days. With highest sodium zirconium cyclosilicate maintenance doses, the proportions with serum bicarbonate <22 mM declined from 39% at baseline to 4.9% at 29 days ($P=0.005$).

- Both hypo- and hyperkalemia are associated with increased cardiovascular and overall mortality, and with ESKD risk, although these associations do not define cause.
- Patiromer and sodium zirconium cyclosilicate are effective and safe for the treatment of chronic hyperkalemia and allow continued use or up-titration of RAAS blocking agents

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