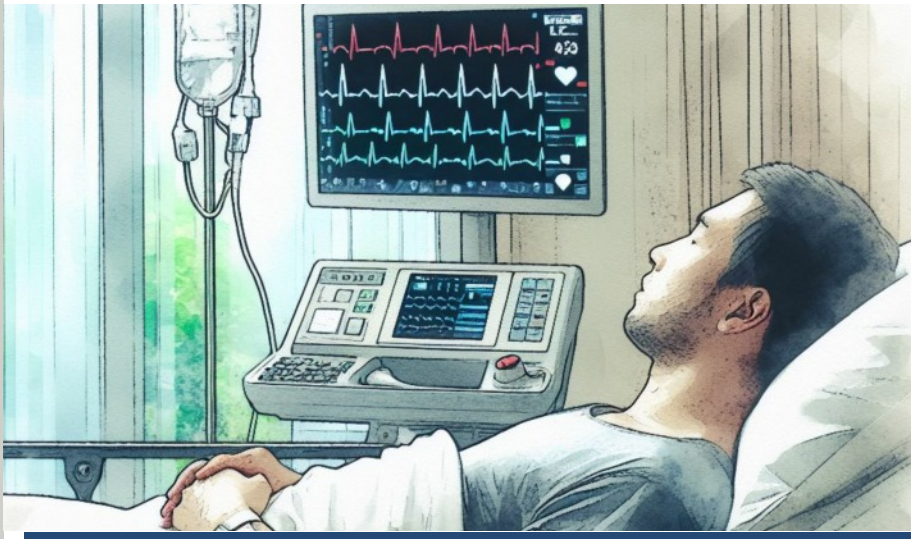
# You Asked for It! CE



# ACUTE AND CHRONIC HYPERKALEMIA: TREATMENT OPTIONS, POTASSIUM BINDERS, AND CLINICAL CASES

AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

## EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- Identify foods that cause hyperkalemia
- List medications that cause hyperkalemia
- Compare and contrast medications that manage acute and chronic hyperkalemia
- Determine the best agent to manage hyperkalemia in each case study

After completing the continuing education activity, pharmacy technicians will be able to

- Identify foods that cause hyperkalemia
- List medications that cause hyperkalemia
- Describe the dosing and storage information of patiromer and sodium zirconium cyclosilicate (SZC)
- Describe the steps of the drug prior authorization process

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**ACPE UAN: 0009-0000-24-026-H01-P**
**0009-0000-24-026-H01-T**

**Grant funding: None**
**Cost: FREE**

**INITIAL RELEASE DATE: May 15, 2024**
**EXPIRATION DATE: May 15, 2027**

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**TARGET AUDIENCE:** Pharmacists and pharmacy technicians interested in electrolyte imbalances, diabetes, and preparing prior authorization.

**ABSTRACT:** Hyperkalemia-high potassium levels-is a serious disorder that warrants appropriate treatment. Defined as a serum potassium level greater than 5.5 mEq (mmol/L), hyperkalemia can be asymptomatic or symptomatic. Severe hyperkalemia can cause irregular heart rhythms. Both drugs and foods can cause hyperkalemia. Medications for the management of acute and chronic hyperkalemia include calcium, insulin, beta-agonists, sodium bicarbonate, loop diuretics, and potassium binders. Sodium polystyrene sulfonate (SPS) has been a gold standard for chronic hyperkalemia for several decades. However, sodium overload can be a concern with SPS. Newer drugs such as patiromer and sodium zirconium cyclosilicate offer both safety and effectiveness, but they are costly alternatives. Pharmacists and pharmacy technicians must be prepared to navigate the prior authorization process to seek coverage for these costly alternatives.

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**FACULTY DISCLOSURE:** Dr. Fong has no financial relationships with an ineligible company.

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## INTRODUCTION

Did you know that all living cells need potassium to maintain cellular fluid balance? Potassium has many benefits. First, it helps muscles to contract. Second, it helps maintain blood pressure. Third, it helps regulate bodily fluids inside cells (intracellular). However, having too much potassium (hyperkalemia) may have a negative impact. Hyperkalemia may cause arrhythmia (irregular heart rhythm), which could be life-threatening. Hyperkalemia can be categorized into two main

types: acute and chronic. Patients with chronic kidney disease are especially prone to elevated potassium levels.[1]

Consider these situations:

- Ms. Gonzalez comes to your pharmacy with a prescription for patiromer. The pharmacy technician attempted to bill her insurance, but the drug required prior authorization. What do you do next? What are the elements of a prior authorization process?
- Mr. Williams comes to your pharmacy complaining about edema (swelling due to excess fluid). He has been taking sodium polystyrene sulfonate (SPS). His doctor asks you, the pharmacist, to recommend an alternative to SPS because of the sodium load concern. What would your response be? What would you recommend to replace SPS?

Acute and chronic hyperkalemia continue to present as major medical dilemmas for healthcare professionals. There is no universally accepted guideline to treat them, and there is no universally accepted classification and monitoring frequency for hyperkalemia. Newer potassium binders, such as patiromer and sodium zirconium cyclosilicate (SZC), may allow optimal use of renin-angiotensin-aldosterone system inhibitor (RAASi) therapy in patients with hyperkalemia. However, these newer therapies are costly alternatives to traditional treatment.

Helping patients navigate the health insurance prior authorization process to seek coverage is a challenging task for pharmacists and pharmacy technicians. If a patient comes to your pharmacy with a prescription for a potassium binder, are you fully equipped to provide the patient with information regarding dosing, storage, and insurance authorization?

Simply put, hyperkalemia is a general medical term that describes a higher-than-normal potassium level in the blood. Normally, a person's extracellular (outside the cells/in the blood) potassium concentration falls between 3.5 to 5 mmol/L. Mild, moderate, and marked hyperkalemia are defined as potassium levels between 5 to 5.9 mmol/L, 6 to 7 mmol/L, and exceeding 7.0 mmol/L, respectively. While mild hyperkalemia requires monitoring and diet restriction, moderate and severe hyperkalemia may cause cardiac complications.[2]

## Epidemiology of Hyperkalemia

Hyperkalemia is a common occurrence. A 2016 American study of 194,456 outpatients found that over a 3-year period, 10.8% of patients had potassium levels greater than 5 mEq/L and 2.3% of the patients had potassium levels greater than 5.5 mEq/L.[3] A 2017 study conducted in a large Swedish healthcare system followed 364,955 participants over three years.[4] The researchers defined hyperkalemia as potassium exceeding 5 mmol/L and moderate/severe hyperkalemia as potassium exceeding 5.5 mmol/L. Hyperkalemia occurred in 25,461 individuals (7%), and 9,059 individuals (2.5%) had moderate/severe hyperkalemia.[4]

Elevated potassium levels are more common in patients with chronic kidney disease (CKD) than in patients without CKD. One study involving four clinical centers and 820 patients in the United States (U.S.) found that 8% of patients with CKD had hyperkalemia.[5] A study involving 55,266 patients with glomerular filtration rate (GFR) less than 60 (an indicator of kidney dysfunction) enrolled in a managed care organization in the U.S. found that 5% of patients had potassium levels at or exceeding 5.5 mEq/L and 20% experienced potassium levels at or exceeding 5 mEq/L.[5] A French study involving 1,038 patients found that 17% of those with stage 2 through 5 CKD had potassium levels at or exceeding 5 mEq/L.[5] An additional study that enrolled 36,359 patients with stage 3 or 4 CKD found that 3% had potassium levels at or exceeding 5 mEq/L.[5]

## Hyperkalemia's History

Sir Humphry Davy at the Royal Institution in London first isolated potassium in 1807 using electrolysis of dry molten caustic potash (KOH, potassium hydroxide). Potassium is an alkali metal and silvery-white in color. It consists of 19 electrons and 19 protons. At 20°C, it has a density of 0.862 g/cm. Potassium is present in all meats, plants, and dairy products and is abundant in fruits and vegetables.[6]

Potassium is important for maintaining cellular function. All cells have a sodium-potassium ATPase (Na+ -K+ ATPase) exchanger, which is partially responsible for maintaining the membrane potential. This serves as a basis for conduction of nerve impulse and stabilization of blood pressure.[7] A diet rich in potassium has been associated with reducing blood pressure, lowering the risk of stroke and nephrolithiasis (kidney stones), and improving bone health.

The body maintains potassium homeostasis through various means. Total body potassium content is achieved by alterations in renal (kidney) excretion of potassium in response to potassium intake. Insulin and beta-adrenergic tone (responsiveness of the autonomic nervous system) help regulate extracellular and intra-

cellular content of potassium.[7] In short, extreme low and high potassium levels are not compatible with life.

**PAUSE and PONDER:** Did you know that a higher-than-normal potassium level (hyperkalemia) can cause neuromuscular symptoms such as muscle cramps and cardiovascular symptoms such as irregular heartbeat? What causes hyperkalemia?

## Causes and Clinical Manifestations

Hyperkalemia has many causes, including but not limited to, tissue injury, insulin deficiency, exercise, medications, and excess dietary potassium intake[8,9]:

- Trauma, massive hemolysis (destruction of red blood cells), and tumor lysis (rapid breakdown of cancer cells) may cause tissue injury, which in turn may cause hyperkalemia.
- Insulin deficiency may cause hyperkalemia. Insulin regulates glucose concentration in the plasma and also causes potassium to move into cells until the kidneys have sufficient time to excrete the dietary potassium load and re-establish total-body potassium content.
- During exercise, potassium is released from skeletal muscle cells and accumulates in the interstitial compartment (a small space in a tissue or between parts of the body), where it exerts a vasodilatory effect (widening of blood vessels).
- Medications may cause hyperkalemia by interfering with the renin-angiotensin-aldosterone system (RAAS). RAAS is a normal cascade that functions in the homeostatic control of arterial pressure, tissue perfusion, and extracellular volume. While many medications may offer cardiovascular benefits by deregulating the RAAS, they can cause concurrent hyperkalemia because the RAAS facilitates potassium excretion in the kidneys.
- Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), beta-blockers (e.g., atenolol, metoprolol, propranolol), cyclosporine, and tacrolimus may cause hyperkalemia by impairing the release of renin.
- Angiotensin-converting-enzyme inhibitors (ACEi) such as benazepril, captopril, enalapril, lisinopril, perindopril, and quinapril block the formation of angiotensin II. Angiotensin-receptor blockers (ARBs) such as azilsartan, candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan prevent angiotensin II from binding to its adrenal receptor. Both mechanisms contribute to the development of hyperkalemia.
- Heparin causes hyperkalemia by interfering with aldosterone biosynthesis in the adrenal gland.
- Amiloride, pentamidine, triamterene, and trimethoprim block sodium reabsorption in the collecting tubule and reduce the negative potential of the lumen. By doing so, they reduce potassium secretion from the kidneys.
- Spironolactone and eplerenone prevent aldosterone from binding with its receptor and increase the likelihood of hyperkalemia.


Excess potassium intake contributes the development of hyperkalemia. **Table 1** (on pages 4 and 5 ) lists foods and their elemental potassium contents. Patients with CKD should adhere to a low potassium diet, but patients often find this difficult in real-world scenarios.[10] In addition, potassium-rich diets (foods with more than 200 mg per serving are considered potassium-rich) have numerous health benefits including blood pressure reduction, reduction in risk of CKD progression, and cardiovascular disease and stroke prevention. A low potassium diet may present a treatment dilemma because it may prevent patients from receiving these benefits.[10]

To prevent hyperkalemia, limited dietary potassium intake is necessary. Patients who are diagnosed with hyperkalemia or at risk of developing hyperkalemia should limit potassium intake from all sources including food, salt substitutes, and supplements to about 40 to 60 mEq (mmol) per day.[11]

**PAUSE AND PONDER:** In a reported case, an individual chewed and ingested burnt match heads in a condition called cautopyreiophagia. This resulted in a plasma potassium concentration of 8 mmol/L and contributed 80 mmol of daily potassium intake. What signs of hyperkalemia did he probably experience?

Hyperkalemia is usually asymptomatic. However, neuromuscular and cardiac abnormalities may develop as hyperkalemia worsens. Neuromuscular manifestations of hyperkalemia can include paresthesia (tingling or prickling) and fasciculations (muscle twitching) in the arms and legs.[8] Severe hyperkalemia can cause paralysis that leads to flaccid quadriplegia (paralysis of all four limbs).[8] In addition to neuromuscular abnormalities, hyperkalemia may lead to electrocardiogram (ECG) changes. Hyperkalemia causes ECG changes in a dose-dependent manner[13]:

- Potassium levels between 5.5 to 6.5 mEq/L: ECG will show tall, peaked T waves
- Potassium levels between 6.5 to 7.5 mEq/L: ECG will show loss of P waves
- Potassium levels between 7 to 8 mEq/L: ECG will show widening of the QRS complex
- Potassium levels between 8 to 10 mEq/L: ECG will produce cardiac arrhythmias, sine wave pattern, and asystole

These cardiac abnormalities can lead to dysrhythmias and death.[13]

| Table 1. Potassium Content of Selected Common Food and Salt Substitutes[12] | | |
|---|---|---|
| **Food** | **Elemental Potassium Content** | |
| | **Milligrams (mg)** | **Milliequivalents (mEq)*** |
| Milk | 350 | 9 |
| Apricot (5) | 480 | 12 |
| Avocado | 300 | 7 to 10 |
| Banana | 451 | 12 |
| Cantaloupe (1/4) | 412 | 11 |
| Kiwi | 252 | 6 |
| Nectarine | 288 | 7 |
| Orange | 300 | 7 |
| Papaya (1/4) | 390 | 10 |
| Peach | 305 | 8 |
| Prunes, 5 dried | 365 | 9 |
| Raisins (1/2 cup) | 553 | 14 |
| Watermelon (1/16) | 560 | 14 |
| *Juices (serving size 4oz = 1/2 cup = 120ml)* | | |
| Apple juice | 148 | 4 |
| Grapefruit juice | 210 | 6 |
| Orange juice, frozen | 252 | 7 |
| Pineapple juice | 148 | 4 |
| Prune juice | 301 | 8 |
| Tomato juice | 225 | 6 |
| *Nuts (serving size 1oz = 30 g)* | | |
| Almonds, dry roasted | 210 | 5 |
| Cashews | 187 | 4 |
| *Salt substitutes (serving size ¼ cup)* | | |
| Examples: NoSalt, Nu-Salt | 610-795 | 15-20 |

*(Table continued on next page)*

## TREATING HYPERKALEMIA

In acute hyperkalemia, patients with potassium levels exceeding 6 mmol/L or patients have who hyperkalemia with any new ECG changes should be referred to a healthcare facility with cardiac monitoring. Kidney Disease: Improving Global Outcomes (KDIGO) recommends monitoring vital signs and cardiac changes.[14] In hyperkalemic patients with ECG changes, KDIGO recommends treatment with calcium chloride, insulin, and beta-agonists. In patients with concomitant metabolic acidemia (lower blood pH), KDIGO recommends sodium bicarbonate. Subsequently, KDIGO considers the use of potassium-binding drugs and loop diuretics. KDIGO suggests dialysis in cases of persistently elevated potassium concentrations exceeding 6 mmol/L or ECG changes that are unresponsive to medical management.[14]

### Treatment of Acute Hyperkalemia

Acute hyperkalemia is generally defined as a serum potassium concentration exceeding the upper limit of normal that is not known to be chronic.[14] Currently, clinicians use no universal classification or monitoring for hyperkalemia. Similarly, no universally accepted treatment guidelines for acute and chronic hyperkalemia exist. Clinicians should not initiate treatment of acute hyperkalemia solely based on serum level of hyperkalemia; they should also consider patients' clinical manifestations (e.g., ECG changes). Treatment options for acute hyperkalemia may include intravenous calcium gluconate, insulin, inhaled beta-agonists, intravenous sodium bicarbonate, and dialysis. **Table 2** (on-page 6) expounds on these treatment options.[11]

Intravenous calcium gluconate for acute hyperkalemia works by stabilizing membrane potential and normalizing ECG changes to prevents irregular heart rhythm. However, it does not lower serum potassium levels. It's duration of effect ranges from 15 minutes to one hour. It may cause adverse effects such as local irritation, hypercalcemia (elevated calcium levels), hypotension

| Table 1. Potassium Content of Selected Common Food and Salt Substitutes (Continued)[12] | | |
|---|---|---|
| **Food** | **Elemental Potassium Content** | |
| | **Milligrams (mg)** | **Milliequivalents (mEq)*** |
| *Vegetables (Serving size 8 oz = 1 cup = 240ml)* | | |
| Acorn squash, cooked | 896 | 23 |
| Beets | 530 | 13 |
| Broccoli, frozen, cooked | 332 | 9 |
| Brussel sprouts, cooked | 494 | 13 |
| Butternut squash, cooked | 583 | 15 |
| Collards, frozen, cooked | 427 | 11 |
| Kidney beans, cooked | 713 | 18 |
| Lentil, cooked | 731 | 19 |
| Lettuce, 1 head Boston | 419 | 10 |
| Mushrooms | 550 | 14 |
| Pinto beans, cooked | 800 | 20 |
| Potato, baked with skin | 844 | 21 |
| Potato without skin | 600 | 15 |
| Pumpkin, canned | 506 | 12 |
| Soybeans, cooked | 972 | 24 |
| Spinach, raw or cooked | 838 | 21 |
| Split peas, cooked | 710 | 18 |
| Sweet potato, baked with skin | 350 | 9 |
| Tomato | 251-273 | 7 |
| White navy beans, cooked | 669 | 18 |
| Zucchini, cooked, sliced | 456 | 12 |
| *Also equivalent to millimoles (mmol) | | |

(low blood pressure), and bradycardia (slowed heart rate). If no effect is observed in five minutes, another dose may be given.[10]

Intravenous insulin works by shifting potassium from extracellular to intracellular space. It has an onset of 15 to 30 minutes and a duration of four to six hours. It may cause hypoglycemia (low blood sugar) and hypokalemia (low potassium levels). Clinicians typically give intravenous insulin with glucose to prevent hypoglycemia during acute hyperkalemia treatment.[10]

Inhaled beta-agonists act within 30 minutes to redistribute potassium from the extracellular to intracellular space. It has an onset of 30 to 60 minutes and duration of effect from two to four hours. Adverse effects include tachycardia (elevated heart rate), tremor, vasoconstriction (narrowing of blood vessels), and hyperglycemia.[10]

Intravenous sodium bicarbonate is another option to treat acute hyperkalemia. It lowers serum potassium levels by increasing potassium elimination through the urine. It has an onset of action of 30 minutes to four hours and a duration of effect of approximately two hours. Possible adverse events include hypocalcemia, metabolic alkalosis (elevated blood pH), hypernatremia (elevated sodium), fluid overload, worsening hypertension, and heart failure.[10]

Patients may receive one of two types of dialysis: peritoneal dialysis or hemodialysis. Peritoneal dialysis uses the lining of the abdominal cavity to filter body waste. A surgeon places a catheter in the abdominal cavity. The dialysis solution enters the abdominal cavity through the catheter and will drain out of the abdominal cavity. Hemodialysis, uses a machine to remove excess water and waste products. A machine removes blood from the body and infuses it through a filter. A dialysate solution flows on the other side of the membrane and draws impurities from the blood. Dialysis is an effective treatment for hyperkalemia.[15]

**Pause and Ponder:** SPS used to be the "gold standard" in treating chronic hyperkalemia. What are the newer potassium binders? Are they safe and effective?

## Treatment of Chronic Hyperkalemia

Chronic hyperkalemia is defined as recurrent episodes of elevated serum potassium concentrations.[10] Treatment options include loop diuretics, RAASi dose modification, identification and removal of hyperkalemia-causing medications, and potassium binders.[10]

Loop diuretics—often used for other indications, such as hypertension and heart failure—increase urinary potassium excretion at the collecting duct of the kidney. Providers commonly use furosemide, a loop diuretic, in chronic hyperkalemia. They often prescribe them with thiazides, ACEIs, and ARBs. However, loop diuretics have their limitations. They may cause volume depletion (reduced blood volume) and their effectiveness declines as renal function declines.[11]

Another treatment option for chronic hyperkalemia is the modification of dosage or interruption of RAASi therapy. No generally accepted guidelines regarding this strategy in patients who experience hyperkalemia exist. However, the European Society of Cardiology recommends patients continue or titrate RAASi treatment to optimal doses in the event of mild hyperkalemia levels between 5.1 and 5.5 mEq/L and moderate hyperkalemia levels between 5.6 and 6 mEq/L.[16]

Potassium binders—including SPS, SZC, and patiromer—are one of the most promising treatments for chronic hyperkalemia. In general terms, a patient will consume fluids with potassium binders. Potassium binders bind to potassium in the bowel and exchange with calcium, sodium and/or hydrogen, usually at the colon. The body will then excrete the potassium in the feces.[17] **Table 3** ( next page) displays onset of action, mechanism of action, and common adverse effects of potassium binders.[10] Note that all potassium binders have a relatively slow onset of action, making them inadequate therapies for acute hyperkalemia.

SPS, approved by the Food and Drug Administration (FDA) in 1958, has been the "gold standard" and the lone potassium binder for several decades. Its mechanism of action is potassium binding in exchange for sodium in the gastrointestinal (GI) tract. However, its adverse effect profile is unfavorable and erratic. In fact, the FDA issued a warning for SPS regarding the risk of colonic necrosis (tissue death) and other GI adverse effects when used with sorbitol in 2009.[10]

Patiromer is a potassium binder approved by the FDA in 2015. It works by binding potassium in exchange for calcium in the GI tract. To date, it has not caused serious adverse effects. Most of the adverse effects are GI disorders (e.g., constipation).[10] Approved in 2018 by the FDA, SZC is the newest potassium binder. Its mechanism of action differs from patiromer. It binds potassium in exchange for hydrogen and sodium in the GI tract and its main site of action is in the small and large intestines. No serious adverse effects have been reported. Adverse effects are mild and

**Table 2. A Summary of Treatment Options for Acute Hyperkalemia[11]**

| Treatment Option | Dosage | Advantage(s) | Disadvantage(s) |
|---|---|---|---|
| Intravenous calcium gluconate | 1 gram via IV piggyback (small bag of solution attached to primary infusion line). Repeat in 5 minutes if needed. | Fast onset | Dose not lower potassium level, only normalizes ECG changes |
| Intravenous insulin | 5–10 units or 0.1 units/kg, maximum 10 units | Fast onset, most reliable treatment | Usually given with dextrose to minimize hypoglycemia |
| Inhaled beta-agonists (e.g., Albuterol) | 10–20 mg via nebulizer | Fast onset | Inconsistent effect, nonselective beta-blockers such as propranolol and sotalol may be less effective |
| Intravenous sodium bicarbonate | 50 mEq, which is equivalent to 50 ml of 8.4 % sodium bicarbonate over 5 minutes. Repeat in 30 minutes as needed. | Work best with acidosis (pH < 7.2) | Variable onset of action |
| Dialysis | Treatment given daily or a few days a week | Reliable treatment to remove waste, effective method to attain norkalemia | Extensive equipment and knowledge required to conduct treatment |

ECG, electrocardiogram; IV, intravenous

| Table 3. Selected Characteristics of Available Potassium Binders[10, 20, 18, 19] | | | | |
|---|---|---|---|---|
| **Drug** | **Onset of Action** | **Mechanism of Action** | **Adverse Effects** | **Usual adult starting dose** |
| Patiromer | 7 hours | Potassium binding in exchange for calcium in GI tract | Abdominal discomfort, constipation, diarrhea, nausea, flatulence, Hypomagnesemia | 8.4 grams orally once daily |
| Sodium zirconium cyclosilicate (SZC) | 1–6 hours | Potassium binding in exchange for hydrogen and sodium in GI tract | Constipation, diarrhea, nausea, vomiting, mild-to-moderate edema | 5 grams orally once daily |
| Sodium polystyrene sulfonate (SPS) | 2-6 hours | Potassium binding in exchange for sodium in GI tract | Constipation, diarrhea, nausea, vomiting, gastric irritation, hypomagnesemia, hypocalcemia, edema, hypokalemia, systemic alkalosis, intestinal necrosis | 15 to 60 grams orally daily |
| GI, gastrointestinal | | | | |

usually GI disorders such as constipation.[10] Veltassa (patiromer) comes in single-use packets containing 1 gram, 8.4 grams, 16.8 grams, or 25.2 grams. User should store Veltassa in the refrigerator at 2°C to 8°C (36°F to 46°F).[20]

Lokelma (SZC) comes in packets containing 5 grams or 10 grams. User should store Lokelma at 15°C to 30°C (59°F to 86°F).[18]

## COMPARING PATIROMER AND SZC

Patiromer and SZC are safe and effective treatments for chronic hyperkalemia. They allow for continuance and optimal doses of RAASi in patients who develop hyperkalemia secondary to RAASi use. They also enable patients to experience optimal hemodialysis outcomes and can ease the dietary potassium restriction. Providers select a potassium binder based on safety and efficacy, cost, insurance coverage, and roles in the treatment of chronic hyperkalemia, which are discussed in detail below.

### Cost and Insurance Coverage

Newer potassium binders are costly alternatives to traditional drugs for hyperkalemia. **Table 4** (next page) lists their estimated out-of-pocket costs as of December, 25, 2023 according to GoodRx. The cost difference between patiromer and SZC is relatively small.[21]

Typical monthly costs associated with patiromer and SZC might be unaffordable for many Americans. However, the vast majority of patients have health plan coverage. (Note that the insurance discussions below are current as of January 2023.)

The Humana website reveals that some Humana Medicare plans cover all doses of patiromer at tier 3 (i.e., they are covered with a prior authorization) but some plans do not cover all doses of SZC. These Humana plans include, but are not limited to, Humana Gold Plus HMO H5619-150, Humana Community H7621-002, Humana Gold Plus HMO H5619-148, Humana Walmart Value Rx Plan PDP, Humana Basic Rx Plan PDP, and Humana Premier Rx Plan PDP.[23] (Note that an HMO is a type of insurance with a network of contracted physicians and a PDP is a Medicare Part D prescription drug plan.)

A cursory check on Scan Health Plans website reveals that Scan Medicare plans appear to cover all doses of patiromer at tier 3, while SZC is not on formulary. These Scan health plans include but are not limited to, Village Health, Scan Classic, and Scan Venture. These plans require a prior authorization on patiromer.[24]

The Wellcare website indicates that Wellcare Medicare plans cover patiromer at tier 3 without a prior authorization. These plans include but are not limited to Wellcare Classic PDP, Wellcare Value Script PDP, and Wellcare Medicare RX Value Plus PDP. Interestingly, the Wellcare Dual Align 129 plan covers SZC at tier 1 and it requires no prior authorization. It's important to remember that a covered drug does not mean free. Patiromer's yearly copay costs (what a patient is required to pay) may exceed $2000, and SZC can cost patients more than $1000 annually.[25]

Manufacturers of both SZC and patiromer offer $0 per month copay savings cards. To use these cards, patients must have commercial insurance that does not cover the full prescription cost or be uninsured and responsible for the full prescription cost. Patients who are ineligible for these savings cards include those who are[26,27]

- enrolled in Medicare Part D, Medicaid, Medigap, Veterans Affairs, Department of Defense programs, or TriCare
- Medicare eligible and enrolled in an employer-sponsored group waiver health plan or government-subsidized prescription drug benefit program for retirees

Pharmacy staff can assist cash-paying patients without insurance contact drug manufacturers to inquire about their patient assistance programs.

### *Breaking Down the Prior Authorization Process*

As noted, some health insurance plans require a prior authorization to cover the newer potassium binders such as patiromer and SZC. This means the insurance company requires extra steps to determine whether a specific medical treatment, procedure, medication, or service is medically necessary and covered under a patient's health insurance plan. Pharmacists and pharmacy technicians can initiate the prior authorization process. Familiarity with the prior authorization process for various insurance plans is imperative for pharmacy staff. Although insurance plans have different forms and requirements within the prior authorization process, the basic steps are the same.

The major steps of the prior authorization process are as follows:

1. Download prior authorization forms from the insurance company website to determine what they require
2. Collect laboratory values, medical history, diagnosis, medical justification, drug history, rationale for request, and other pertinent patient information
3. Complete the prior authorization forms
4. Fax completed prior authorization forms to the insurance company or upload them via online platforms
5. Start the appeal process if denied

Pharmacists can enlist pharmacy technicians' help to perform most or all of these steps.

The prior authorization process can take up anywhere from one day to more than a week. It is important to explain to patients that a prior authorization requirement does not mean a medication is not covered. It simply means that the insurance company might need more information before it covers the medication.

Pharmacy staff can sometimes initiate an appeal process if the insurer denies the medication. The most common reason for rejection/denial is insufficient supporting information. The other common reason for rejection/denial is drug class exclusion. For example, some Medicare part D plans do not cover certain drug classes. Once the provider or pharmacy submits an appeal, the insurance company usually takes one to two days to respond. Remember that manufacturer sponsored patient assistance programs can help patients who cannot afford the copay and patients who do not have insurance, and pharmacy staff can help patients with enrollment.

**Table 5** (next page) lists the contact information for selected insurance plans. However, most tasks or inquiries can be handled online.

## Safety and Efficacy of Patiromer

The phase 2, multicenter, open-label, randomized AMETHSYT-DN trial determined patiromer starting doses for a phase 3 study and evaluated the long-term safety and efficacy of patiromer in 306 outpatients with hyperkalemia. The mean reduction from baseline in serum potassium level at week 4 or time of first dose titration in patients with mild hyperkalemia was 0.35, 0.51, and 0.55 mEq/L for groups starting at 4.2 g twice daily, 8.4 g twice daily, and 12.6 g twice daily, respectively.[29] For patients with moderate hyperkalemia, the reduction was 0.87, 0.97, and 0.92 mEq/L for patients starting at 8.4 g twice daily, 12.6 g twice daily, and 16.8 g twice daily, respectively.[29]

From week four through week 52, AMETHYST-DN researchers observed statistically significant mean decreases in serum potassium levels. Over the 52-week-long trial, hypomagnesemia (7.2%) was the most common treatment-related adverse event and mild to moderate constipation (6.3%) was the most common GI adverse event. The researchers concluded that patiromer starting doses of 4.2 to 16.8 g twice daily resulted in statistically significant decreases in serum potassium levels after four weeks of treatment, lasting through 52 weeks.[29]

The OPAL-HK clinical trial assessed the safety and efficacy of patiromer with an initial treatment phase and a withdrawal phase.[30] Among 237 patients in the initial treatment phase, the mean change in serum potassium level was -1.01 mmol per liter. Among 107 patients in the randomized withdrawal phase, the median increase in potassium levels from baseline of that phase

**Table 4. Estimated Out-of-Pocket Costs of Patiromer and SZC[22]**

| Drug | Units | Cost |
|---|---|---|
| Patiromer | 8.4 g x 4 Packs | $ 181.53 |
| | 8.4 g x 30 Packs | $ 940.61 – 989.34 |
| | 16.8 g x 30 Packs | $ 940.61 – 989.34 |
| | 25.2 g x 30 Packs | $ 940.61 – 989.34 |
| Sodium zirconium cyclosilicate (SZC) | 10 g x 11 | $ 289.27 – 324.67 |
| | 10 g x 30 | $ 782.16 – 871.05 |
| | 5 g x 11 | $ 289.40 – 324.67 |
| | 5 g x 30 | $ 781.61 – 782.16 |

| Table 5. Contact Information on Selected Insurance Plans[28,23-25] | | |
|---|---|---|
| **Plan** | **Department** | **Phone number** |
| Humana | Humana Clinical Pharmacy Review Department | 800-555-2546 |
| Express Scripts | Express Scripts Coverage Review Department | 800-753-2851 |
| Scan | Medical Reviews Department | 844-424-8886 |
| WellCare | Pharmacy Appeals Department | 855-538-0453 |

was greater with placebo than with patiromer. The most common adverse effect in the initial treatment phase was constipation (11%), followed by diarrhea (3%), hypomagnesemia (3%), and nausea (3%). The most common adverse effects of the randomized withdrawal phase in the patiromer group were headache, supraventricular extra systoles (heart rhythm irregularities), constipation, diarrhea, and nausea; all occurred in 4% of all patients.[30]

## Safety and Efficacy of SZC

The phase 3, multicenter, randomized, double-blind, placebo-controlled HARMONIZE clinical trial evaluated SZC's efficacy and safety for 28 days in outpatients with hyperkalemia at 44 sites in the U.S., Australia, and South Africa over six months.[31] Patients received 10 g of SZC three times daily in the initial 48-hour open-label phase. Of the 258 patients, 237 patients achieved normokalaemia (normal potassium levels) with levels between 3.5 and 5 mEq/L and were randomized to receive SZC 5 g, 10 g, or 15 g or placebo daily for 28 days. In the open-label phase, serum potassium levels declined from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 hours. In the randomized phase, serum potassium was significantly lower during days 8 through 29 with all SZC doses compared to placebo. Adverse events were comparable between SZC and placebo. Edema occurred more often in the 15 g group. Compared with placebo, all three doses of SZC resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days.[31]

The double-blind, placebo-controlled, phase 3b multicenter DIALIZE study evaluated SZC for the management of hyperkalemia in patients undergoing hemodialysis.[32] The researchers randomized adults with end-stage renal disease (ESRD) who were managed with hemodialysis three times weekly to SZC or placebo. These patients had pre-dialysis hyperkalemia and received SZC 5 g once daily on non-dialysis days. The researchers titrated doses to maintain normokalaemia over four weeks in 5 g increments to a maximum of 15 g. About 41.2% of patients in the SZC group responded to treatment compared with 1% of the 99 patients receiving placebo. Serious adverse events occurred in 7.3% of patients in the SZC group and 8.1 % of patients in the placebo group.[32]

# CASE STUDIES

Hyperkalemia usually occurs as a result of other illnesses. Certain medical conditions such as advanced stages of CKD, heart failure, hypertension, diabetes, myocardial infarction, and/or any combinations of these conditions increase the risk of hyperkalemia.[10] Treating the underlying diseases may alleviate the severity of hyperkalemia. While it's critical to treat the whole patient, certain comorbidities are of utmost importance, including those imposing the greatest risks of morbidity and mortality. The key is to prioritize treatments according to the risks. Heart diseases, stroke, diabetes, and kidney diseases ranked first, fifth, eighth, and tenth, respectively, in the top 10 leading causes of death in the U.S. in 2021.[33]

## Case Study #1

Joan Smith is a female patient born on June 18, 1956. She has been diagnosed with type 2 diabetes, ESRD, osteoarthritis, hypertension, atrial fibrillation, and hyperkalemia. Dr. Bach contacted the pharmacist to conduct a comprehensive medication therapy management (MTM) and suggest an alternative to replace SPS.

Below is a list of selected recent lab values for Joan:

| Item | Result | Units | Interval |
|---|---|---|---|
| $A_1C$ | 9.6 (H) | N/A | < 6.5 |
| BUN | 28 (H) | mg/dL | 8 – 27 |
| Creatinine | 2.3 (H) | mg/dL | 0.76 – 1.27 |
| Potassium | 5.3 (H) | mmol/L | 3.5 – 5.2 |
| Sodium | 145 (H) | mmol/L | 134 – 144 |
| Chloride | 99 | mmol/L | 96 – 106 |
| Carbon dioxide | 26 | mmol/L | 20 – 29 |
| Calcium | 9.1 | mg/dL | 8.6 – 10.2 |
| Protein, total | 8.2 (H) | g/dL | 6.8 – 8.0 |
| Albumin (A) | 5.0 (H) | g/dL | 3.8 – 4.8 |
| Globulin (G), total | 3.3 | g/dL | 1.5 – 4.5 |
| A/G ratio | 1.6 | N/A | 1.2 – 2.2 |
| Bilirubin, total | 0.4 | mg/dL | < 1.2 |
| $A_1C$, hemoglobin A1C; BUN, blood urea nitrogen | | | |

(*Case 1 continues on the next page)*

Joan is taking the following medications:

- NPH/regular human insulin 70/30 50 units subcutaneously twice daily
- Lisinopril 20 mg orally once daily
- SPS 60 mL orally as needed
- Nephro-Vite 1 tablet orally once daily
- Apixaban 5 mg orally twice daily
- Aspirin 81 mg orally once daily
- Ibuprofen 600 mg orally three times daily

Joan's $A_1C$ is out of range, so she would benefit from tighter blood sugar control. The pharmacist recommended changing NPH/regular human insulin (70/30) to lispro 16 units subcutaneously three times daily before meals and glargine 50 units subcutaneously once daily at bedtime. For Joan's osteoarthritis, changing ibuprofen to acetaminophen 650 mg by mouth every eight hours is prudent because ibuprofen, an NSAID, may precipitate the development of hyperkalemia. While NSAIDs are not contraindicated in patients with kidney disease, clinicians should use the lowest dose possible for the shortest duration and avoid using NSAIDs at all in patients with severe kidney disease. Clinicians can consider a topical NSAID for mild osteoarthritis pain in smaller joints.[34] Joan had mild hyperkalemia as indicated by her laboratory result. Her elevated BUN and creatinine values indicate that her renal function is insufficient. Joan's sodium level is also elevated at 145 mmol/L. Both SPS and SZC can cause sodium overload, so they might not be the most appropriate choice for Joan. It may not be prudent to discontinue or reduce Joan's lisinopril dose (RAASi therapy). Joan was advised to follow up with Dr. Bach at the next office visit.

After a thorough teleconference with Dr. Bach, the pharmacist recommends starting patiromer with an initial dose of 8.4 g once daily after discontinuing the SPS. Upon consultation with the patient and her caregiver, the technician reminds them to store patiromer in the refrigerator at 2°C to 8°C (36°F to 46°F). If stored at room temperature (25°C ± 2C° [77°F ± 4°F]), they must use the patiromer within three months. For either storage condition, they must not use patiromer after the expiration date printed on the packet and avoid exposing it to excessive heat greater than 40°C (104°F).[20]

In addition, the pharmacist inquired about Joan's use of over-the-counter herbal medications. The pharmacist informed Joan that certain herbal medications or supplements such as noni juice may cause or exacerbate hyperkalemia.[35] Unconventional over-the-counter traditional Chinese medicines such as dried skin of toads (Chinese name: Chan Su) may cause poisoning and result in hyperkalemia.[36]

## Case study #2

John Williams is a male patient born on August 29, 1965. He has been diagnosed with hyperkalemia, ESRD, hyperlipidemia, type 2 diabetes, erectile dysfunction, hypertension, and heart failure. His most recent lab values are presented below.

| Item | Result | Units | Interval |
|---|---|---|---|
| $A_1C$ | 11.1 (H) | N/A | < 6.5 |
| BUN | 29 (H) | mg/dL | 8 – 27 |
| Creatinine | 2.45 (H) | mg/dL | 0.76 – 1.27 |
| Potassium | 4.8 | mmol/L | 3.5 – 5.2 |
| Sodium | 135 | mmol/L | 134 – 144 |
| Chloride | 98 | mmol/L | 96 – 106 |
| Carbon dioxide | 27 | mmol/L | 20 – 29 |
| Calcium | 11.0 (H) | mg/dL | 8.6 – 10.2 |
| Protein, total | 8.2 (H) | g/dL | 6.8 – 8.0 |
| Albumin (A) | 5.1 (H) | g/dL | 3.8 – 4.8 |
| Globulin (G), total | 3.4 | g/dL | 1.5 – 4.5 |
| A/G ratio | 1.5 | N/A | 1.2 – 2.2 |
| Bilirubin, total | 0.5 | mg/dL | < 1.2 |
| $A_1C$, hemoglobin A1C; BUN, blood urea nitrogen | | | |

John is taking the following medications:

- Patiromer 16.8 mg orally once daily
- Metoprolol succinate ER 100 mg orally once daily
- Simvastatin 40 mg orally once daily
- Sildenafil 50 mg orally as needed for sexual activity
- Sacubitril-valsartan 97-103 mg orally twice daily
- Spironolactone 100 mg orally once daily
- Insulin glargine 40 units subcutaneously at bedtime
- Insulin lispro 14 units subcutaneously 15 minutes before each meal
- Semaglutide 2 mg subcutaneously once weekly
- Empagliflozin 25 mg orally once daily
- Calcifediol 30 mg orally once daily

John first experienced high sodium levels while on SPS due to the sodium load per dose. Subsequently, John was prescribed patiromer and experienced stomach upset. Dr. Kidd contacts the pharmacist to conduct a comprehensive MTM and suggest an alternative to replace patiromer.

John's potassium level was within range and his condition has been stable. However, the calcium level (11.0 mg/dL) is elevated. Patiromer might not be the most appropriate choice. The pharmacist recommended considering SZC. John can start on an initial dose of 10 g orally 3 times daily for 48 hours, followed by 10 g once daily thereafter. Sacubitril-valsartan (RAASi therapy) reduces the risk of hospitalization and spironolactone substantially lowers the risk of both morbidity and death among patients with

severe heart failure.[37] As a result, the pharmacist recommended that John remain on sacubitril-valsartan and spironolactone as prescribed.

John's glucose level ($A_1C$) was out of range at 11.1. He would benefit from continuous glucose monitoring (CGM). The pharmacist introduced a commercially available CGM device to John and encouraged him to monitor his glucose level after meals, at bedtime, and at any time John feels there is a need to monitor. To reach $A_1C$ target, John should titrate his basal insulin (glargine) by increasing 2 units every three days and prandial insulin (lispro) by 1 to 2 units twice weekly without hypoglycemia.

The pharmacist asked John about the use of salt substitutes and advised him that some salt substitutes may cause hyperkalemia. Regarding erectile dysfunction, John stated that sildenafil was, "…working somewhat but I need a bit more help. My sex life is not what it used to be. Maybe I can purchase something over-the-counter to spice it up!" The pharmacist discouraged the use of commercially available over-the-counter aphrodisiacs containing digoxin-like substances. Atrial fibrillation, ventricular fibrillation, and death have been reported with their use.[38]

## CONCLUSION

No universally accepted guidelines exist for monitoring and classification of hyperkalemia. Similarly, no universally accepted guidelines exist for dosage modification of RAASi therapy. When selecting drugs to treat hyperkalemia, healthcare professionals should consider factors such as co-existing diseases, duration of action, onset of action, cost, drug interactions, food interactions, cardiovascular benefits, and renal benefits. Newer potassium binders may help optimize RAASi therapy and provide a safe and reliable chronic hyperkalemia treatment option. The use of these newer potassium binders and the optimal use of RAASi therapy may improve cardiovascular outcomes.

### Figure 1. Safety and Counseling for Hyperkalemia

**Best**

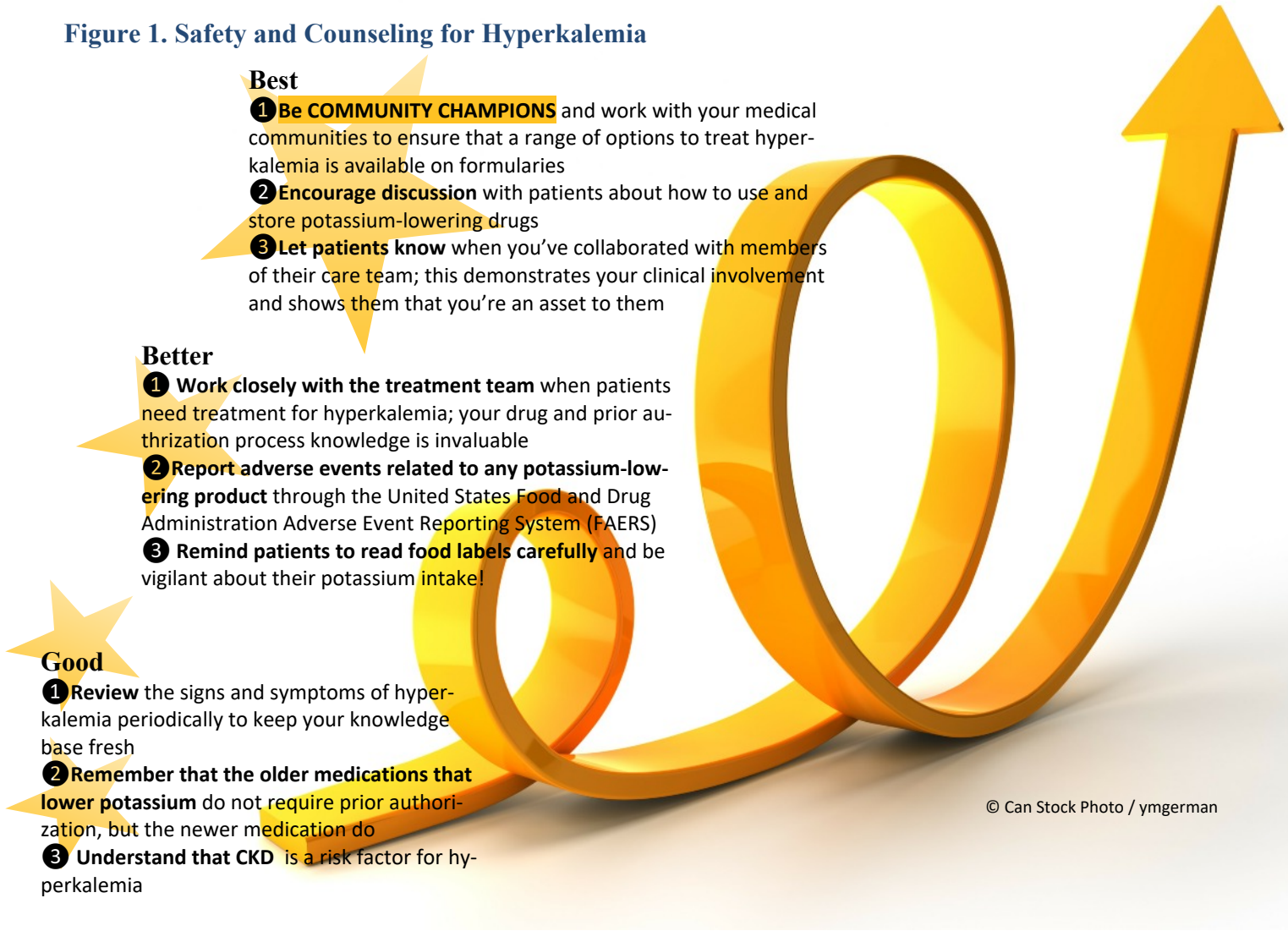
1. **Be COMMUNITY CHAMPIONS** and work with your medical communities to ensure that a range of options to treat hyperkalemia is available on formularies
2. **Encourage discussion** with patients about how to use and store potassium-lowering drugs
3. **Let patients know** when you've collaborated with members of their care team; this demonstrates your clinical involvement and shows them that you're an asset to them

**Better**

1. **Work closely with the treatment team** when patients need treatment for hyperkalemia; your drug and prior authrization process knowledge is invaluable
2. **Report adverse events related to any potassium-lowering product** through the United States Food and Drug Administration Adverse Event Reporting System (FAERS)
3. **Remind patients to read food labels carefully** and be vigilant about their potassium intake!

**Good**

1. **Review** the signs and symptoms of hyperkalemia periodically to keep your knowledge base fresh
2. **Remember that the older medications that lower potassium** do not require prior authorization, but the newer medication do
3. **Understand that CKD** is a risk factor for hyperkalemia



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