Optimizing the Management of Hyperkalemia:
An Update for Health-System Pharmacists

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Overview of Hyperkalemia

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Learning Agenda

- Review potassium homeostasis
- Identify factors promoting potassium shifts including the renin-angiotensin-aldosterone system (RAAS)
- Discuss etiologies and risk factors associated with hyperkalemia
- Describe electrocardiogram (ECG) changes associated with hyperkalemia
Hyperkalemia

- Defined as a serum potassium level above the reference range, >5.0 mEq/L
- Associated with muscle weakness, paralysis, and life-threatening effects on cardiac conduction
- Incidence and prevalence rates are reported between 1 and 10 per 100 patients.
- A hyperkalemic episode in a CKD patient increases the odds of mortality within 1 day of the event.

<table>
<thead>
<tr>
<th>Hyperkalemia Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
</tr>
<tr>
<td>2–3</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease.

All-Cause Mortality Associated with Serum Potassium Levels in Non-Dialysis-Dependent Patients with Chronic Kidney Disease ($n = 1227$)
Potassium Homeostasis

Factors Stimulating Potassium Shifts

<table>
<thead>
<tr>
<th>Factors</th>
<th>Potassium Shifts</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF to ICF</td>
<td>ICF to ECF</td>
</tr>
<tr>
<td>Insulin release</td>
<td>Mineral acidosis</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Hyperosmolarity</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>Nonselective beta blockade</td>
</tr>
<tr>
<td>Anabolic state</td>
<td>Alpha-1 stimulation</td>
</tr>
</tbody>
</table>

Intracellular (ICF) [K+] 90%
Extracellular (ECF) [K+] 10%

Neuromuscular and cardiovascular excitability

ECF = extracellular fluid; ICF = intracellular fluid.
Potassium Homeostasis

Potassium Intake (100 mEq/day)

- Muscle (2650 mEq)
- ECF (70 mEq)
- RBC (250 mEq)
- Liver (250 mEq)
- Bone (300 mEq)

Potassium Excretion (Kidney = 90 mEq/day; Stool = 10 mEq/day)

Internal balance

External balance

RBC = red blood cell.
For educational purposes only.
Renin-Angiotensin-Aldosterone System

- **Renin inhibitors**
- Angiotensin-converting enzyme (ACE)
  - Kidney releases renin into blood
- Liver releases angiotensinogen into blood
- Angiotensin I
  - In pulmonary blood
- Angiotensin II stimulates aldosterone secretion by adrenal cortex
- Angiotensin II
  - Aldosterone stimulates Na⁺ and H₂O reabsorption in the nephrons
- Angiotensin II stimulates K⁺ reduction
- Aldosterone receptor antagonists
- Sodium reabsorption
- Renin-Angiotensin-Aldosterone System

Electrolyte balance. archive.cnx.org. Available at: http://archive.cnx.org/contents/ca0c80ce-7586-419b-a890-6bdad12ec809@4/electrolyte-balance. For educational purposes only.
Etiologies

Impaired Renal Excretion
- Renal insufficiency or failure

Extrinsic Factors
- Exogenous potassium intake
- Medications

Intracellular to Extracellular Potassium Shift
- Metabolic acidosis
- Hemolytic states
- Tissue damage

Diet
- Orange juice, nectarines, kiwis, raisins, dried fruit, bananas, cantaloupe, honeydew, prunes

Risk Factors

- Age
- Renal insufficiency or CKD
- Diabetes
- Hypertension (HTN)
- Congestive heart failure (CHF)
- High protein intake
- Medications promoting potassium retention
  - Use of RAAS inhibitors (RAASi) – with increased risk if presence of HTN, CKD, or CHF
Hyperkalemia Risk (with and without CKD)

P < .001 for all moderate and severe hyperkalemia groups

P < .05 for Stage 5 with normokalemia vs reference group

Normokalemia <5.5 mEq/L; moderate ≥5.5 mEq/L and <6.0; severe ≥6.0 mEq/L

For educational purposes only.
Conditions

- Hyperkalemia secondary to type IV renal tubular acidosis includes the following:
  - Diabetes mellitus
  - Sickle cell disease or trait
  - Lower urinary tract obstruction
  - Adrenal insufficiency
  - Primary Addison’s disease due to autoimmune disease, tuberculosis, or infarct
  - Enzyme deficiencies
  - Genetic disorders
- Burns (electrical and thermal)
## Agents Causing Hyperkalemia

<table>
<thead>
<tr>
<th>Causes</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that promote transmembrane potassium shift</td>
<td>Nonselective beta-blockers (eg, propranolol, labetalol, carvedilol), digoxin intoxication, mannitol</td>
</tr>
<tr>
<td>Drugs that affect aldosterone secretion</td>
<td>ACE inhibitors (eg, benazepril, lisinopril), direct renin inhibitors (eg, aliskiren), NSAIDs and COX-2 inhibitors (eg, ibuprofen, celecoxib), calcineurin inhibitors (cyclosporine, tacrolimus)</td>
</tr>
<tr>
<td>Drugs that cause tubular resistance to action of aldosterone or renin release</td>
<td>Aldosterone antagonists (eg, spironolactone, eplerenone) and other potassium-sparing diuretics (eg, amiloride, triamterene), trimethoprim, pentamidine, heparin</td>
</tr>
<tr>
<td>Agents that contain potassium</td>
<td>Salt substitutes and alternatives, penicillin G, stored blood products</td>
</tr>
<tr>
<td>Other</td>
<td>Succinylcholine, herbal supplements</td>
</tr>
</tbody>
</table>

COX-2 = cyclooxygenase 2; NSAIDs = nonsteroidal anti-inflammatory drugs.  
Signs and Symptoms

- Frank muscle paralysis
- Dyspnea
- Palpitations
- Chest pain
- Nausea or vomiting
- Paresthesias
ARS Question 1

Which of the following potassium thresholds require treatment?

A. >5 mEq/L
B. 5 mEq/L + clinical symptoms or ECG changes
C. >6.5 mEq/L
D. All of the above are correct.
Pretreatment Potassium Concentrations

![Graph showing the distribution of pretreatment potassium concentrations.](image-url)

*Am J Med Sci.* 2014;347:93-100. For educational purposes only.
Mean Pretreatment Potassium Concentration Prompting Treatment

<table>
<thead>
<tr>
<th>Serum Potassium</th>
<th>Typical ECG Appearance</th>
<th>Possible ECG Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (5.6–6.4 mEq/L)</td>
<td>Peaked T waves</td>
<td>Prolonged PR segment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (6.5–8.0 mEq/L)</td>
<td>Loss of P wave</td>
<td>Prolonged QRS complex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ST-segment elevation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectopic beats and escape rhythm</td>
</tr>
<tr>
<td>Severe (&gt;8.0 mEq/L)</td>
<td></td>
<td>Progressive widening of QRS sine wave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asystole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axis deviations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bundle branch blocks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fascicular blocks</td>
</tr>
</tbody>
</table>

ECG Changes

# Hyperkalemia in Hospitalized Patients

<table>
<thead>
<tr>
<th>No. of ECGs Performed</th>
<th>Potassium Concentration (mEq/L)</th>
<th>No ECG-Related Changes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fordjour KN, Walton TW, Doran JD, et al.</td>
<td>70</td>
<td>≥6.5</td>
</tr>
<tr>
<td>Acker CG, Johnson JP, Palevsky PM, et al.</td>
<td>54</td>
<td>≤6.8</td>
</tr>
</tbody>
</table>

Identification

- Vital signs are usually normal (exceptions: bradycardia or tachypnea).
- Muscle weakness and flaccid paralysis
- Depressed or absent deep tendon reflexes
Identification

Blood samples from a vein or line into which potassium is being infused

Laboratory error

Pseudohyperkalemia (hemolysis, leukocytosis, thrombocytosis)

Repeated clenching of fist during phlebotomy

Uncommon genetic syndromes

Identification

- Investigate pathophysiological mechanisms
- Rule out spurious elevations
- Determine existing predispositions to hyperkalemia
- If absence of contributing factors, repeat blood test
Factors Requiring Treatment

Presence of clinical symptoms

Presence of ECG changes
Laboratory Testing

ECG
Urinary potassium, sodium, osmolality
Complete blood count
Metabolic profile

Glucose level
Digoxin level
Arterial or venous blood gas
Urinalysis
Cortisol and aldosterone levels
Serum uric acid and phosphorus
Serum creatinine phosphokinase
Urine myoglobin

Correcting Hyperkalemia

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Learning Agenda

- Discuss management of underlying causes of hyperkalemia
- Review traditional methods to correct acute and chronic hyperkalemia
- Describe novel agents for treatment of hyperkalemia including patiromer sorbitex calcium and sodium zirconium cyclosilicate (ZS-9)
Treatment of Underlying Cause

- Impaired renal excretion of potassium
  - Supportive care for management of acute and/or chronic kidney disease

- Extrinsic factors
  - Removal of offending agent
  - Discontinuation of exogenous potassium supplementation

- Treatment of disease states that cause extracellular shifting of potassium
  - Acidosis
  - Rhabdomyolysis
  - Tumor lysis syndrome
ARS Question 2

Which of the following medications and mechanisms of action for treatment of hyperkalemia are correctly matched?

A. Sodium bicarbonate AND elimination of potassium
B. Insulin AND intracellular shifting of potassium
C. Calcium gluconate AND elimination of potassium
D. Furosemide AND intracellular shifting of potassium
E. All of the above are correctly matched.
Acute Hyperkalemia

- Singular event constituting a medical emergency
- Characterized by a rapid increase in potassium
- Requires immediate evaluation and rapid reduction in potassium but no ongoing treatment
- Three phases of management
  - Stabilization of myocardium
  - Shifting of potassium to the intracellular space
  - Elimination of potassium

Stabilization of Myocardium

- Obtain and evaluate patient 12-lead ECG
- Prompt administration of IV calcium
  - Stabilizes myocardium by increasing threshold potential thereby preventing ventricular arrhythmias
  - **Does not change potassium concentration**
  - Calcium chloride 1 g IV or calcium gluconate 2–3 g IV
  - Central venous access is preferred for administration of calcium chloride.

*IV = intravenous.*
*Kidney Int. 2016;89:546-554.*
Shifting of Potassium to Intracellular Space

- All agents that shift potassium intracellularly are temporary solutions.

- **Insulin**
  - Insulin regular 10 units IV + dextrose 50% IV 50 mL (25 g)
  - Coadministration of dextrose prevents hypoglycemia.
  - Duration of effect: ~4–6 hours

- **Beta_2 agonists**
  - Albuterol 10–20 mg nebulization
  - Decrease serum K+ by 0.3–0.6 mEq/mL in 30 minutes

- **Sodium bicarbonate**
  - Sodium bicarbonate 50–100 mEq IV x 1 dose
  - Varying data regarding duration of action (~2 hours)

Activate Na/K+ ATPase pumps

Causes Na/H+ exchange, in turn

Elimination of Potassium

- Decrease/eliminate all potassium intake
- Increase urinary elimination
  - Loop diuretics
  - Requires adequate renal function for drug to reach site of action
  - Efficient diuresis is required for sufficient kaliuresis.
- Increase fecal elimination
  - Sodium polystyrene sulfonate (SPS)
- Dialysis
  - Resource intensive
  - Poses risk to patient – particularly those not already on chronic dialysis

*Kidney Int. 2016;89:546-554.*
Sodium Polystyrene Sulfonate

- FDA approval in 1958
- **Mechanism of action**
  - Exchanges sodium ions for potassium ions in the large intestine, which are then excreted in feces
  - Onset of action: 2–24 hours
- **Efficacy**
  - Patient-dependent
  - May decrease K⁺ by up to 0.9 mEq/L
- **Warnings/Precautions**
  - May cause intestinal necrosis and/or fecal impaction, particularly when administered with sorbitol
  - Not appropriate for long-term use

*FDA = US Food and Drug Administration.*
# Acute Hyperkalemia Treatment Summary

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Onset of Action</th>
<th>Duration of Effect*</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium chloride 10% or Calcium gluconate 10%</td>
<td>6.8 mmol elemental calcium (1 g calcium chloride or 3 g calcium gluconate)</td>
<td>IV</td>
<td>1–3 minutes</td>
<td>30–60 minutes</td>
<td>Cardiac membrane potential stabilization</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>50–100 mEq</td>
<td>IV</td>
<td>5–10 minutes</td>
<td>~2 hours</td>
<td>Intracellular shift of K⁺</td>
</tr>
<tr>
<td>Insulin regular</td>
<td>10 units</td>
<td>IV</td>
<td>30 minutes</td>
<td>4–6 hours</td>
<td>Intracellular shift of K⁺</td>
</tr>
<tr>
<td>Albuterol</td>
<td>10–20 mg</td>
<td>Inhalation</td>
<td>30 minutes</td>
<td>2–4 hours</td>
<td>Intracellular shift of K⁺</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>40 mg furosemide or equivalent</td>
<td>IV</td>
<td>5–10 minutes (varies with start of diuresis)</td>
<td>As long as diuresis is present</td>
<td>Renal excretion of K⁺</td>
</tr>
<tr>
<td>Dialysis</td>
<td>N/A</td>
<td>Hemodialysis or CRRT</td>
<td>Within minutes of starting therapy</td>
<td>Patient-dependent</td>
<td>Removal of K⁺</td>
</tr>
</tbody>
</table>

*Duration of effect for agents that eliminate potassium depend on ongoing potassium redistribution and/or ongoing potassium intake.

CRRT = continuous renal replacement therapy; N/A = not applicable.

Chronic Hyperkalemia

- Greater than one event per year requiring ongoing management
- Caused by chronic impairment of potassium excretion
- Patients at greatest risk
  - CKD
  - Receiving medications that cause RAAS inhibition
- Goals of therapy
  - Prevent development and recurrence of hyperkalemia by correcting underlying cause

Novel Agents for Hyperkalemia

- Patiromer sorbitex calcium
- Sodium zirconium cyclosilicate (ZS-9)
Patiromer Sorbitex Calcium

- FDA approval date: October 21, 2015
- Mechanism of action
  - Non-absorbed, cation-exchange polymer containing a calcium-sorbitol counterion; binds potassium in lumen of GI tract resulting in reduction of potassium levels
- Adult dose
  - 8.4 g PO once daily
  - May increase dose at ≥1-week intervals by 8.4 g (max dose: 25.2 g/day)
- US Boxed Warning
  - Binds to other oral medications leading to possible decreased efficacy of other agents
  - Other oral medications should be administered at least 6 hours before or 6 hours after patiromer.

GI = gastrointestinal; PO = by mouth.
Patiromer Sorbitex Calcium

- **Precautions**
  - Avoid use in patients with severe constipation, bowel obstruction, or impaction
  - May worsen GI conditions

- **Adverse effects**
  - Hypomagnesemia (5%–9%)
  - Constipation (7%), diarrhea (5%), abdominal distress/flatulence (2%)

- **Average wholesale price**
  - 8.4 g (4): $142.80
  - 16.8 g (1): $23.80
  - 25.2 g (1): $23.80

### OPAL-HK

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Two-phase, single-blind, randomized withdrawal study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>243 patients with CKD and hyperkalemia receiving ≥1 RAAS-inhibiting drug</td>
</tr>
</tbody>
</table>
| Intervention       | Phase 1: Patiromer x 4 weeks titrated to maintain K+ 3.8–5.1 mEq/L  
|                    | Phase 2: One arm crossover to placebo to evaluate persistence of effect; remaining patients continued on patiromer for 4 additional weeks |
| Outcomes           | Primary outcome: reduction in potassium at 4 weeks and 8 weeks |
| Results            | Phase I: reduction of 1.01 mEq/L in overall population (P < .001)  
|                    | Phase II: recurrence 60% in placebo vs 15% in patiromer group (P < .001) |

**Reduction of potassium in OPAL-HK phase I**

*N Engl J Med. 2015;372:211-221. For educational purposes only.*
# Patiromer – Clinical Efficacy & Safety Data

## PEARL-HF

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, double-blind, placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>N = 105; patients had indication for spironolactone therapy + either CKD with GFR &lt;60 mL/min OR history of hyperkalemia that led to discontinuation of a RAASi</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>Severe GI disorders, unstable arrhythmias, obstructive or restrictive cardiomyopathy, ACS, TIA, QTc &gt;500 ms, receiving or anticipating needing dialysis, SBP &gt;170 or &lt;90, LFTs &gt;3 x ULN</td>
</tr>
<tr>
<td>Intervention</td>
<td>Randomized to patiromer 30 g once daily or placebo for 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Spironolactone initiated on day 1 and titrated to 25 mg on day 15 if potassium is ≤5.1 mEq/L</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Serum potassium levels at 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Incidence of hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Rate of successful titration of spironolactone</td>
</tr>
<tr>
<td>Results</td>
<td>Serum potassium reduced by 0.45 mEq/L more in patiromer vs placebo (P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td>Incidence of hyperkalemia 7.3% patiromer vs 24.5% placebo (P =.015)</td>
</tr>
<tr>
<td></td>
<td>Proportion of patients having successful up-titration of spironolactone: 91% vs 74% (P = .019)</td>
</tr>
<tr>
<td></td>
<td>Incidence of hyperkalemia in CKD patients: 6.7% vs 38.5% (P = .041)</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; GFR = glomerular filtration rate; LFT = liver function test; SBP = systolic blood pressure; TIA = transient ischemic attack; ULN = upper limit of normal.  
Sodium Zirconium Cyclosilicate (ZS-9)

- **FDA status**: pending
- **Mechanism of action**
  - Selective cation exchanger that binds potassium in exchange for hydrogen and sodium ions
- **Dose range studied**: 1.25–15 g PO once daily
- **Adverse effects**
  - Mild GI effects (nausea, diarrhea, constipation, abdominal pain)
  - Mild edema and hypokalemia in high-dose groups when studied
**ZS-9 – Clinical Efficacy & Safety Data**

<table>
<thead>
<tr>
<th><strong>Sodium Zirconium Cyclosilicate in Hyperkalemia</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
</tr>
<tr>
<td><strong>Population</strong></td>
</tr>
</tbody>
</table>
| **Intervention** | Stage 1: ZS-9 or placebo TID for 48 hours  
Stage 2: patients with normokalemia were randomized to either ZS-9 or placebo once daily for the remaining 2 weeks |
| **Outcomes** | Exponential rate of change in mean potassium at 48 hours |
| **Results** | • Mean reduction in potassium at 48 hours was -0.3 mEq/L.  
• Potassium remained at 4.7 and 4.5 mEq/L for the 5-g and 10-g groups, respectively. |
| **AEs** | GI effects (2%–8%) |

**Reduction of potassium in ZS-9 phase III trial**

AE = adverse effects; TID = 3 times a day.  
# ZS-9 – Clinical Efficacy & Safety Data

<table>
<thead>
<tr>
<th><strong>HARMONIZE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
</tr>
<tr>
<td><strong>Population</strong></td>
</tr>
</tbody>
</table>
| **Intervention** | • All patients received ZS-9 10 g PO TID x 48 hours during initial open-label period.  
  • Normokalemia was achieved in 237 patients who were then randomized to ZS-9 5, 10, 15 g or placebo once daily x 28 days.  
  • 65% CKD patients, 35% heart failure; >50% remained on RAAS-inhibiting therapy |
| **Outcomes** | Serum potassium levels at 48 hours and 28 days |
| **Results** | • At 48 hours, mean reduction in potassium = 1.1 mEq/L ($P < .001$).  
  • At 28 days, all doses of ZS-9 resulted in significant decrease in potassium and maintenance of reduction ($P < .001$ for all groups).  
  • More patients on placebo returned to hyperkalemia during 28-day period. |
| **Adverse Effects** | Similar between ZS-9 and placebo groups; hypokalemia developed in the 10-g and 15-g groups |

*Eur J Heart Fail. 2015;17:1050-1056.*
Sodium Zirconium Cyclosilicate (ZS-9)

- **Mechanism of action**: Selective cation exchanger that binds potassium in exchange for hydrogen and sodium ions.
- **Dose range studied**: 1.25 – 15 g PO once daily.
- **Adverse effects**: Mild gastrointestinal effects (nausea, diarrhea, constipation, abdominal pain), mild edema and hypokalemia in high dose groups when studied.

**STATUS**

- **May 27, 2016**: FDA sent Complete Response Letter (CRL) to AstraZeneca.
  - Cited observations in a preapproval manufacturing inspection.
  - Acknowledged receipt of additional material that required review.
- **October 18, 2016**: AstraZeneca submitted complete resubmission of NDA to FDA for sodium zirconium cyclosilicate.

NDA = New Drug Application.

## Comparison of Potassium-Binding Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Onset of Action</th>
<th>Potassium-Lowering Effect</th>
<th>FDA Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium polystyrene sulfonate</td>
<td>15 g given 1–4 times daily</td>
<td>PO/rectal</td>
<td>3–4 hours</td>
<td>-0.9 mEq/L in 24 hours</td>
<td>Yes (1958)</td>
</tr>
<tr>
<td>Patiromer sorbitex calcium</td>
<td>8.4 g once daily, titrated weekly (maximum dose: 25.2 g)</td>
<td>PO</td>
<td>Not defined</td>
<td>-1.01 mEq/L over 4 weeks</td>
<td>Yes (2015)</td>
</tr>
<tr>
<td>Sodium zirconium cyclosilicate (ZS-9)</td>
<td>Studied in doses of 1.25, 2.5, 5, and 10 g</td>
<td>PO</td>
<td>2–3 hours</td>
<td>-1.1 mEq/L in 48 hours</td>
<td>No (NDA resubmitted October 2016)</td>
</tr>
</tbody>
</table>

Adapted from: *Pharmacy Times.* 2016:109-117.
Role in Therapy for Novel Agents

- Both agents have been shown to be effective in reducing and preventing hyperkalemia in patients with CKD and heart failure.
  - Included patients remaining on RAAS-inhibiting therapy
- May have a role in prevention and treatment of chronic hyperkalemia, allowing patients to remain on RAAS-inhibiting therapy
- Continuation of ACE inhibitors, ARBs, and/or spironolactone may enable patients to retain clinical outcome benefits proven with these medication classes.
Future Directions for Novel Agents

- Long-term safety and efficacy are unclear due to short duration of clinical trials.
  - Patiromer: maximum duration 8 weeks
  - ZS-9: maximum duration 28 days
- Additional trials are needed to assess clinical outcomes when patients are able to continue RAAS-inhibiting therapy.
  - CKD: cardiovascular-related mortality, progression of CKD
  - Heart failure: decreased HF hospitalizations, decreased mortality
- Further trials are needed to assess safety when used for longer durations.

Pharmacist Strategies to Optimize Hyperkalemia Outcomes

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Hyperkalemia Management - Four Steps

1. Antagonize the effects of hyperkalemia
2. Identify and remove sources of potassium
3. Decrease serum potassium levels by promoting intracellular shifts
4. Remove potassium from the body
# Hyperkalemia Treatments

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Potassium Reduction (mEq/L)</th>
<th>Clinical Pearls</th>
</tr>
</thead>
</table>
| Calcium chloride 10% or calcium gluconate 10% | 6.8 mmol elemental calcium (1 g calcium chloride or 3 g calcium gluconate) | N/A                        | Does not affect potassium concentrations  
Can worsen digoxin toxicity  
Effective in normocalcemic patients  
Must give infusion in patients that do not have a central line. |
| Sodium bicarbonate                             | 50–100 mEq                  | 0.7                        | When administered by infusion, effect is delayed.  
Significant sodium load  
Can worsen acidosis in patients with respiratory insufficiency |
| Insulin regular                                 | 10 units                    | 0.6–1.0                    | Give 50 mL of 50% dextrose 5% for normoglycemic patients (blood glucose <250 mg/dL).  
Consider 5% dextrose solution infusion to prevent hypoglycemia with repeated doses. |
## Hyperkalemia Treatments

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Potassium Reduction (mEq/L)</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>10–20 mg</td>
<td>0.62–0.98</td>
<td>Underdosing is common. Dose necessary for potassium reduction is 2–8 times that given via nebulizer and 50–100 times the dose by metered dose inhalers.</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>40 mg furosemide or equivalent</td>
<td>—</td>
<td>Caution in volume-depleted patients Limited efficacy in moderate-to-severe kidney disease</td>
</tr>
<tr>
<td>Dialysis</td>
<td>N/A</td>
<td>Dialysis dependent</td>
<td>Barriers: time, access (in nondialysis patients), invasive nature</td>
</tr>
</tbody>
</table>
A Pharmacist’s Role in Hyperkalemia

- Identifying patients at risk
  - Clinical decision tools
  - Flags within electronic health record
- Treatment recommendations
  - Indirect
    - Hyperkalemia kits in automated dispensing cabinets
    - Order sets
  - Direct
    - Clinical recommendations during direct patient care
    - Participation in code/resuscitation events
- Prevention of recurrence
  - Identifying potential cause
  - Pharmacotherapy recommendations
  - Role of novel agents?
Case Study 1

JM is a 64-year-old female with history of HTN, diabetes, GERD, CHF (EF = 30%), and left leg ulcer, now with purulent secretions and pain in lower extremities. She reports poor intake due to not feeling well for the past 2 days. Upon admission, examination and testing reveals the following:

<table>
<thead>
<tr>
<th>Laboratory Results</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium 132 mEq/L</td>
<td>Amlodipine 5 mg PO daily</td>
</tr>
<tr>
<td>Potassium 5.8 mEq/L</td>
<td>Carvedilol 25 mg PO twice daily</td>
</tr>
<tr>
<td>BUN 34 mg/dL</td>
<td>Lisinopril 40 mg PO daily</td>
</tr>
<tr>
<td>Serum creatinine 1.9 mg/dL</td>
<td>Spironolactone 25 mg PO twice daily</td>
</tr>
<tr>
<td>Glucose 316 mg/dL</td>
<td>Metformin 500 mg PO twice daily</td>
</tr>
<tr>
<td></td>
<td>Multivitamin PO once daily</td>
</tr>
<tr>
<td></td>
<td>Pantoprazole 40 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>Furosemide 20 mg PO daily</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen; EF = ejection fraction; GERD = gastroesophageal reflux disease.
What risk factors does JM have for hyperkalemia?

- Renal insufficiency
- Diabetes
- Medications: beta-blocker and RAASi
- HTN and CHF (in the presence of RAASi)
Discussion Question

What additional information would be helpful to determine if treatment is necessary?

- ECG
- Vital signs
- Arterial blood gas
- Compliance with medications
ARS Question 3

Would you treat JM’s hyperkalemia?

A. Absolutely
B. Not at all
C. Maybe, depending on more information
# Management

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Onset of Action</th>
<th>Duration of Effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium chloride 10% or calcium gluconate 10%</td>
<td>6.8 mmol elemental calcium (1 g calcium chloride or 3 g calcium gluconate)</td>
<td>IV</td>
<td>1–3 minutes</td>
<td>30–60 minutes</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>50–100 mEq</td>
<td>IV</td>
<td>5–10 minutes</td>
<td>~2 hours</td>
</tr>
<tr>
<td>Insulin regular</td>
<td>10 units</td>
<td>IV</td>
<td>30 minutes</td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Albuterol</td>
<td>10–20 mg</td>
<td>Inhalation</td>
<td>30 minutes</td>
<td>2–4 hours</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>40 mg furosemide or equivalent</td>
<td>IV</td>
<td>5–10 minutes (varies with start of diuresis)</td>
<td>As long as diuresis is present</td>
</tr>
<tr>
<td>Dialysis</td>
<td>N/A</td>
<td>Hemodialysis or CRRT</td>
<td>Within minutes of starting therapy</td>
<td>Patient-dependent</td>
</tr>
</tbody>
</table>

*Duration of effect for agents that eliminate potassium depend on ongoing potassium redistribution and/or ongoing potassium intake.

Medication Management

- Initiate treatment with regular insulin ± calcium administration
- Recheck blood glucose
- Follow up basic metabolic panel to confirm potassium reduction
- Perform detailed medication history with compliance status
- Determine if modifications to current medication regimen are necessary
DM is a 58-year-old male with HTN, CKD Stage 3 (baseline SCr: 2.1), and hyperlipidemia. He presented to the ED today with altered mental status, reported decreased oral intake, and nausea. Per his wife, his blood pressure control has been poor on only one agent and his primary care physician recently prescribed lisinopril 20 mg once daily in addition to his prior HTN regimen. Shortly after arrival in the ED, DM has a cardiac arrest and you are the pharmacist responding to the code.

**Laboratory Results**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>136 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>6.9 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>56 mg/dL</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>3.7 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>138 mg/dL</td>
</tr>
</tbody>
</table>

**Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine 5 mg PO daily</td>
<td>Renal multivitamin PO daily</td>
</tr>
<tr>
<td>Atorvastatin 40 mg PO daily</td>
<td>Omeprazole 20 mg PO daily</td>
</tr>
<tr>
<td>Lisinopril 20 mg PO daily (started 10 days prior)</td>
<td>Tamsulosin 0.4 mg PO daily</td>
</tr>
</tbody>
</table>

12-lead ECG: tachycardic, peaked T waves, widened QRS

ED = emergency department; SCr = serum creatinine.
What risk factors does DM have for hyperkalemia?

A. HTN
B. CKD
C. Lisinopril use
D. B & C
E. All of the above
ARS Question 5

What initial therapy would you recommend for DM?

A. Sodium zirconium cyclosilicate (ZS-9)
B. Calcium gluconate 2 g IV x 1 dose
C. Sodium polystyrene sulfonate (SPS)
D. Furosemide 40 mg IV x 1 dose
Case 2 – Part 2

DM was successfully resuscitated following 1 round of CPR, calcium gluconate 2 g IV x 1 dose, insulin regular 10 units IV x 1 dose, and dextrose 25 g IV x 1 dose. He also received 3 L of 0.9% NaCl for fluid resuscitation. He was admitted to the ICU for monitoring post-cardiac arrest, however was extubated the following day, is hemodynamically stable, and discharge planning has begun. The team involves you as their clinical pharmacist to help with outpatient medication management.

<table>
<thead>
<tr>
<th>Laboratory Results</th>
<th>Vital Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>T</td>
</tr>
<tr>
<td>Potassium</td>
<td>BP</td>
</tr>
<tr>
<td>BUN</td>
<td>HR</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>RR</td>
</tr>
<tr>
<td>Glucose</td>
<td>O₂ Sat</td>
</tr>
</tbody>
</table>

BP = blood pressure; CPR = cardiopulmonary resuscitation; HR = heart rate; ICU = intensive care unit; NC = nasal cannula; RR = respiration rate; T = temperature.
ARS Question 6

What is your recommendation regarding DM’s HTN and CKD management?

A. Never restart ACE inhibitor; initiate ARB instead
B. Restart lisinopril now but at a lower dose
C. Restart lisinopril now at lower dose AND initiate patiromer
D. Wait until SCr completely back to baseline, then restart lisinopril at a lower dose and consider addition of patiromer
E. Avoid use of ACE inhibitors and ARBs and choose a different class of medication for BP management
Summary

- Identifying patients at risk
  - Clinical conditions
  - Medications
- Treatment recommendations
- Prevention of recurrence
  - Identifying potential cause
  - Pharmacotherapy recommendations
  - Role of novel agents
    - Patiromer sorbitex calcium
    - Sodium zirconium cyclosilicate