# ACUTE KIDNEY INJURY (AKI)

- AKI is characterized by an abrupt decrease in renal function over hours to days, resulting in:
  (1) accumulation of nitrogenous waste products, BUN and creatinine (azotemia), and
  (2) the inability to maintain and regulate fluid, electrolyte, and acid-base balance.
- Treatment goals include preventing complications of AKI (e.g., hyperkalemia) and reversing the decline in kidney function to prevent progression to CKD.

AKI is defined as a functional or structural kidney abnormality that manifests with the following indices:

(1) an increase in sCr of 0.3 mg/dL or greater within 48 hours, OR
(2) an increase in sCr of 1.5 or greater times baseline within 7 days, OR
(3) UOP (urine output) < 0.5 ml/kg/hour for 6 hrs
  - oliguria (UOP < 400 ml/day)
  - anuria (UOP < 50 ml/day)

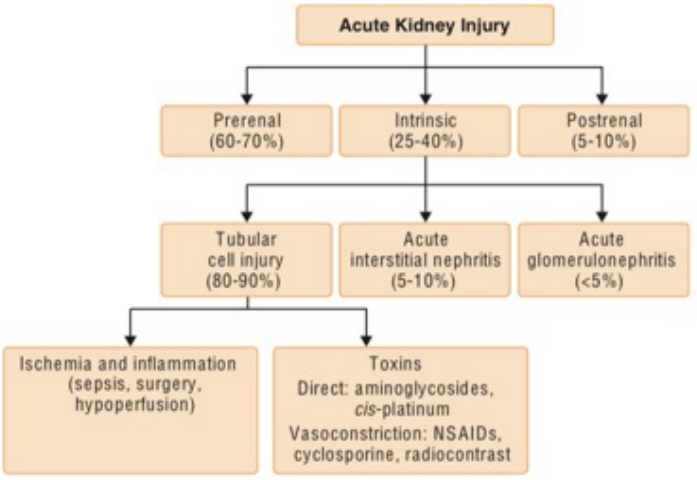
The stages of AKI (i.e., KDIGO classification) depend on the degree of kidney dysfunction, based on sCr levels and reduction in UOP (up to anuria).

**TABLE 112-1 KDIGO ACUTE KIDNEY INJURY CLASSIFICATION**

| STAGE | SERUM CREATININE | URINE OUTPUT |
|---|---|---|
| 1 | 1.5-1.9 times baseline<br>OR<br>≥0.3 mg/dL (≥26.5 µmol/L) increase | <0.5 mL/kg/hr for 6-12 hr |
| 2 | 2.0-2.9 times baseline | <0.5 mL/kg/hr for ≥12 hr |
| 3 | 3.0 times baseline<br>OR<br>Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) | <0.3 mL/kg/hr for ≥24 hr<br>OR<br>Anuria for ≥12 hr |

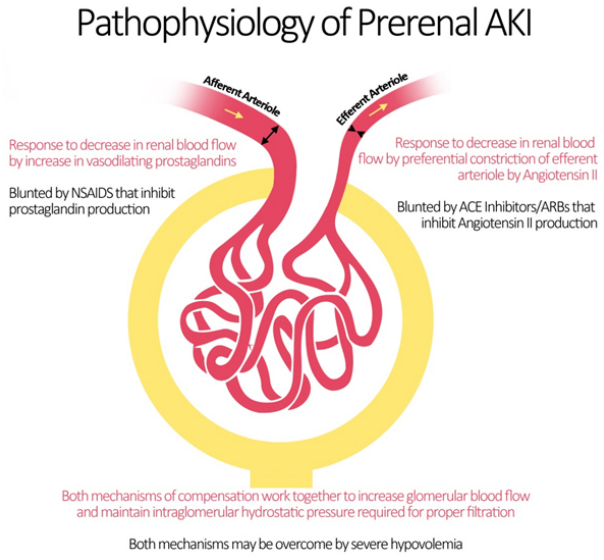
## Causes of Acute Kidney Injury (AKI)

The causes of AKI are divided into 3 anatomic categories: (1) prerenal, (2) intrinsic, (3) postrenal




## I. Prerenal Azotemia

- most common cause of AKI (60-70%)
- caused by kidney hypoperfusion due to hypovolemia (bleeding, sepsis, over-diuresis) or due to reduced renal perfusion (CHF, sepsis, NSAIDs, ACEi, ARBs)
- NSAIDs reduce glomerular perfusion by constricting afferent arterioles and RAS blockers (ACEi's, ARBs) reduce glomerular perfusion by dilating efferent arterioles.




## II. Intrinsic Causes of AKI

- Intrinsic AKI is subdivided into 3 categories: tubular disease, interstitial disease, and glomerular disease.

(1) Tubular: Acute Tubular Necrosis (ATN) – (80-90%)
  - ATN is the most common cause of intrinsic AKI and is usually caused by ischemia and nephrotoxins.
    - ischemia may be caused by hypotension, hypovolemia, septic shock → hypoperfusion of kidneys → ATN
    - nephrotoxins may cause direct tubular toxicity or vasoconstriction of renal vessels, or both.

- <u>nephrotoxins</u> (cont.)
  - Aminoglycosides, vancomycin, chemo agents --> cause direct tubular toxicity.
  - NSAIDs, cyclosporin --> constrict afferent arterioles --> reduce glomerular perfusion.
  - RAS blockers (ACEi's, ARBs) --> dilate efferent arterioles --> reduce intraglomerular hydrostatic pressure.
  - Radiographic contrast-induced nephrotoxicity (CIN) appears to be caused by both, renal vasoconstriction and direct nephrotoxic effects --> ATN.
    - CIN risk factors include: DM, CKD, CHF, age, concomitant use of other nephrotoxic drugs (NSAIDs, RAS blockers)
    - CIN prophylaxis: 1-3 ml/kg (500-1000 ml) of NS over 6 hours before and after contrast administration

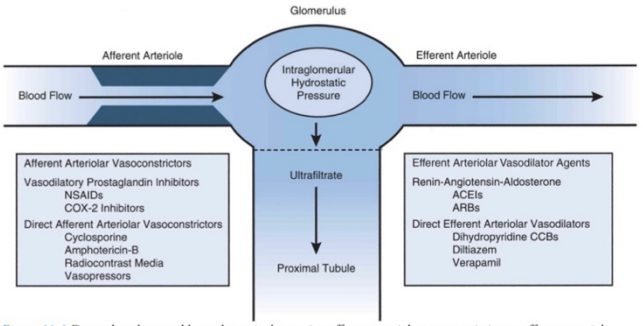
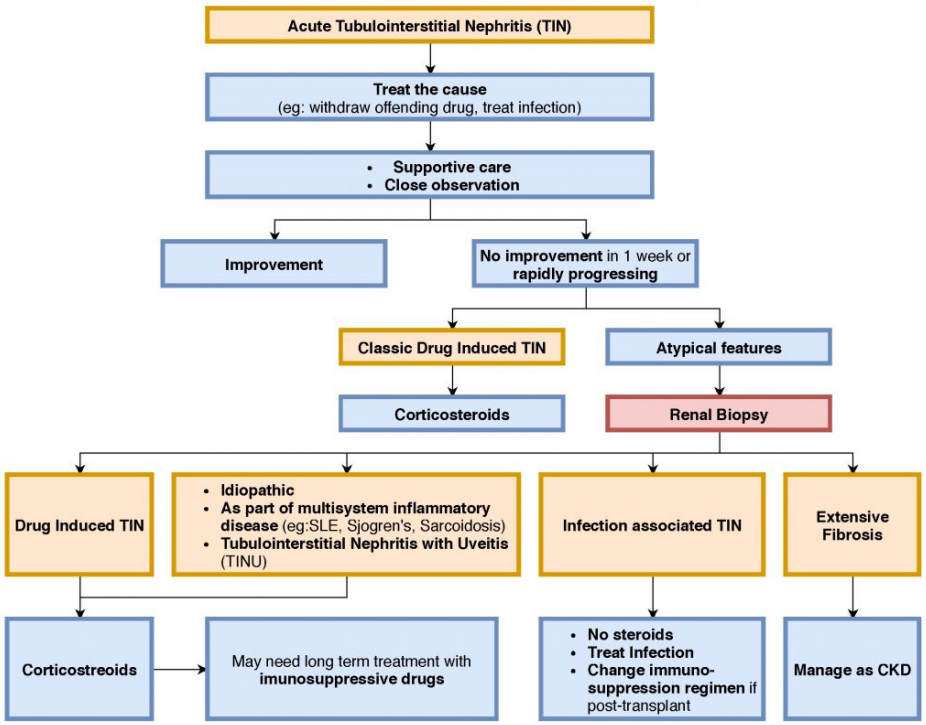


Figure 29-2 Drugs that alter renal hemodynamics by causing afferent arteriole vasoconstriction or efferent arteriole vasodilation. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium-channel blockers; COX-2, cyclo-oxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

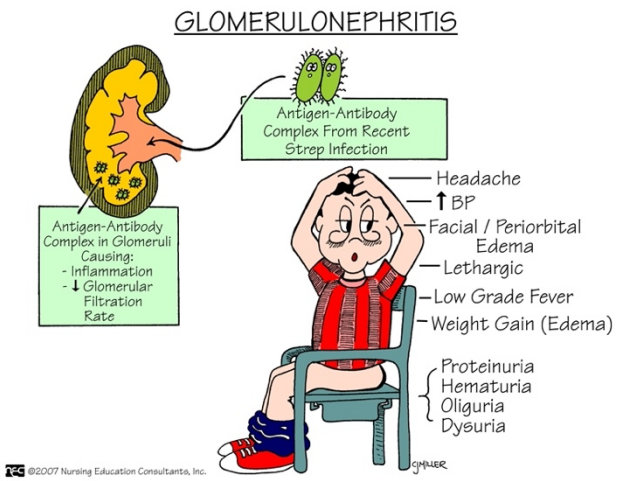
(2) <u>Interstitial: Acute Interstitial Nephritis (AIN)</u>
or <u>Acute Tubulointerstitial Nephritis (TIN)</u> – (5-10%)

- TIN is characterized by inflammation and interstitial edema, mainly caused by drugs (70%): penicillin, cephalosporins, sulfonamides, diuretics, allopurinol, and NSAIDs.
- TIN may also be caused by bacterial infections (e.g., pyelonephritis), viral infections, and immunologic disorders (e.g., Lupus).
- Treatment consists of supportive measures:
  - infections --> initiate antimicrobial / antiviral therapy
  - drug-induced AIN --> removal of offending drug
  - immunologic disorders (e.g., Lupus) → initiate a short 2-week course of corticosteroid taper with prednisone, starting with 1 mg/kg (60 mg) x 3 days ….



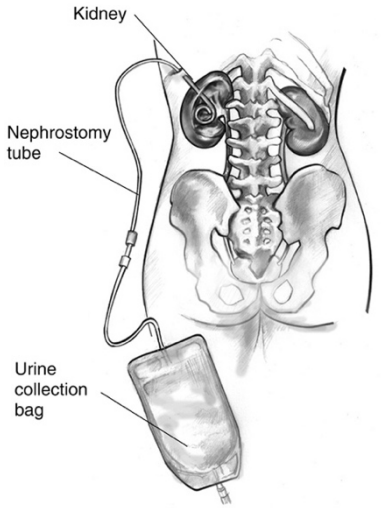
(3) Glomerular: Acute Glomerulonephritis (5%)

- The pathogenesis of GN includes infectious agents (e.g., streptococcus) or deposition of immune complexes in autoimmune diseases such as SLE (systemic lupus erythematosus) → inflammation → decreased GFR.
- GN is characterized by hypertension, proteinuria, hematuria, oliguria (UOP < 400 ml/day).
- GN is diagnosed with a renal biopsy.
- Treatment generally involves the use of corticosteroids treatment with prednisone in a 2-week tapering schedule.




## III. Postrenal Acute Kidney Injury (5-10% of AKI)

- Postrenal AKI is due to obstructed urinary flow and can be detected with renal ultrasound
- Postrenal AKI includes benign prostatic hypertrophy (BPH), prostate cancer, cervical cancer, nephrolithiasis.
- BPH can be corrected by placement of a bladder catheter
- Neoplastic process usually requires ureter stenting or placement of a percutaneous nephrostomy tube.
- Postrenal AKI usually resolves rapidly after the obstruction has been removed.




## Treating Complications of AKI: Hyperkalemia

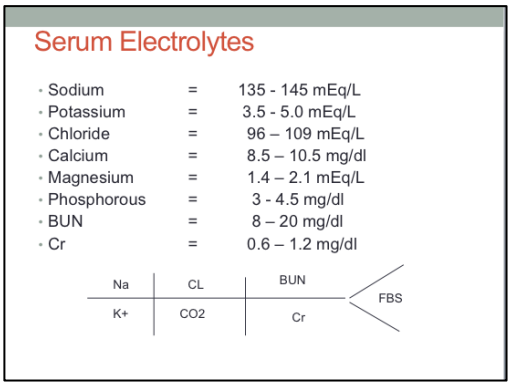
- Management of hyperkalemia depends on its severity and clinical symptoms.
  - Patients with AKI and K > 6.5 or those with symptoms of hyperkalemia (i.e., muscle weakness, paralysis, cardiac conduction abnormalities, cardiac arrhythmias) should be treated urgently.
  - Patients with AKI and K > 5.5 should also be treated urgently if there's ongoing tissue breakdown (rhabdomyolysis) or ongoing K absorption (e.g., GI bleeding).

**TABLE 17-17 Causes of Hyperkalemia**

| | |
|---|---|
| Pseudohyperkalemia | Tourniquet use<br>Hemolysis (in vitro)*<br>Leukocytosis<br>Thrombocytosis |
| Intracellular to extracellular potassium shift | Acidosis*<br>Heavy exercise<br>β-Blockade<br>Insulin deficiency<br>Digitalis intoxication<br>Hyperkalemic periodic paralysis |
| Potassium load | Potassium supplements<br>Potassium-rich foods<br>IV potassium<br>Potassium-containing drugs<br>Transfusion of aged blood<br>Hemolysis (in vivo)<br>GI bleeding<br>Cell destruction after chemotherapy<br>Rhabdomyolysis/crush injury*<br>Extensive tissue necrosis |
| Decreased potassium excretion | Renal failure*<br>Drugs—potassium-sparing diuretics,* β-blockade, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, cyclosporine, tacrolimus<br>Aldosterone deficiency*<br>Selective defect in renal potassium excretion (pseudohypoaldosteronism, systemic lupus erythematosus, sickle cell disease, obstructive uropathy, renal transplantation, type IV renal tubular acidosis) |

- Patients with chronic mild hyperkalemia (K ≤ 5.5) or chronic moderate hyperkalemia (K = 5.5 – 6.5) due to CKD or patients who use RAS blockers do not require urgent lowering of serum $K^+$. Treatment (tx) options include:
  - discontinuation of RAS blockers (ACEi's, ARBs)
  - discontinuation of NSAIDs
  - dietary modifications (less than 2 gm $K^+$ per day)
  - treatment with diuretics (thiazide, Loop diuretics)
  - treatment of chronic metabolic acidosis (e.g., sodium bicarbonate 1 gm tabs)
- Urgent tx of hyperkalemia (K ≥ 6.5) is directed at accomplishing the following objectives:
  - antagonizing the membrane effects of $K^+$ with calcium gluconate or calcium chloride
  - driving extracellular $K^+$ into the cells with dextrose 50% 25 GM IV + Reg insulin 10 units IV
  - removing excess $K^+$ from the body with diuretics, GI cation exchangers, or dialysis

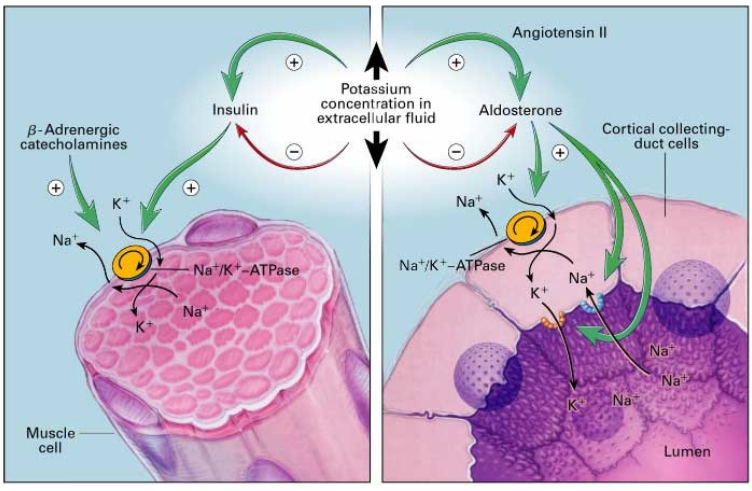
## Calcium Gluconate (CaGluc)




- Calcium directly antagonizes the membrane actions of hyperkalemia since hypocalcemia increases cardiotoxicity of hyperkalemia.
- The effect of IV calcium begins within minutes, with a short duration of 30-60 mins; therefore, calcium should be combined with other therapies that drive $K^+$ into cells.
- Calcium can be given every 30-60 mins as long as serum calcium level is not elevated.
- CaGluc dose: 1000 mg infused over 2-3 minutes
- $CaCl_2$ (calcium chloride) dose: 500 – 1000 mg infused over 2-3 minutes.
  - $CaCl_2$ contains 3 times more elemental calcium compared with CaGluc
  - $CaCl_2$ is irritating to veins and may cause tissue necrosis if the IV infiltrates or leaks into surrounding tissue (i.e., extravasation)
  - $CaCl_2$ should be administered into a central or deep vein to prevent vascular irritation and the potential for extravasation. CaGluc may be given via a peripheral vein.
- Note: Calcium should not be mixed with intravenous bicarbonate-containing solutions, since calcium carbonate precipitation occurs.

## Regular Insulin with Dextrose

- MOA: insulin lowers serum $K^+$ by activating the Na-K-ATPase pump in skeletal muscle
- Dextrose (D-glucose) 50% 50 ml (25 gm dextrose) is given IVP first, then regular insulin 10 units IV
  - if BG ≥ 250 mg/dL, insulin should be given without glucose
  - BG levels are taken every hour for 5-6 hours after giving insulin to prevent hypoglycemia



## Regular Insulin with Dextrose (cont.)

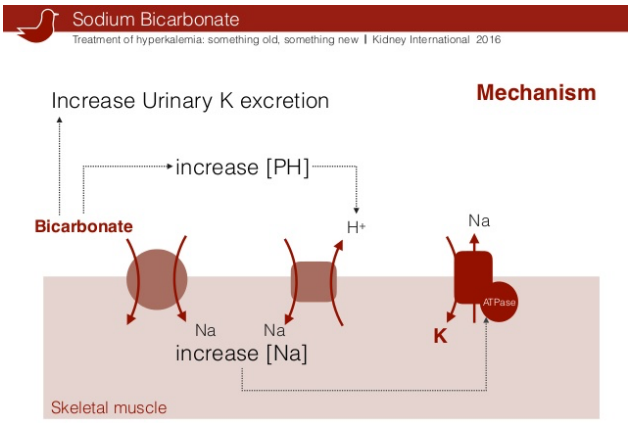
- The effect of insulin begins in 10-20 minutes and peaks at 30-60 mins, and lasts 4-6 hours.
- In most patients, dextrose 25 GM IV + Regular insulin 10 units decreases serum $K^+$ by 0.5 – 1.2 mEq/L.
- Regular insulin with dextrose 50% may be given every 2-4 hours with careful BG monitoring.

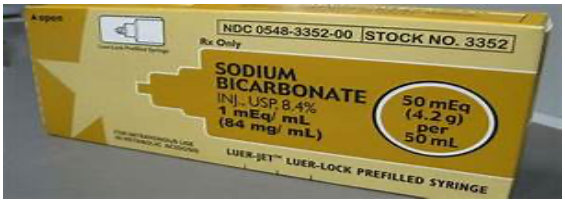
## Albuterol (Beta-2 Agonist)

- Albuterol drives $K^+$ into cells by increasing the activity of the Na-K-ATPase pump in skeletal muscle.
- Dose: albuterol 10 – 20 mg in 4 ml saline delivered by nebulizer over 10 mins (Note: albuterol dose is 4-8 times the dose used for bronchodilation the treatment of asthma / COPD)
- Albuterol lowers serum $K^+$ by 0.5 to 1.5 mEq/L.
- Albuterol demonstrates an additive effect when used with Reg. insulin plus dextrose 50% IV, capable of reducing serum $K^+$ by 1.2 to 1.5 mEq/L.
- Albuterol side effects (SE's) include tachycardia, therefore it should be avoided in patients with angina pectoris and atrial fibrillation.

## Sodium Bicarbonate

- MOA: $NaHCO_3$ administration results in $H^+$ release from cells in exchange for $K^+$
- $NaHCO_3$ has limited efficacy in lowering serum K; therefore, it should not be used as the only treatment in acute management of hyperkalemia.
- Bicarbonate therapy in hyperkalemia may also be beneficial in patients with metabolic acidosis.
- A bicarbonate infusion (150 mEq in 1 L of D5W) over 2-4 hours is preferred to giving hypertonic solutions in the standard $NaHCO_3$ ampule of 50 mEq / 50 ml IVP x 3 doses to reduce the risk of inducing hypernatremia.

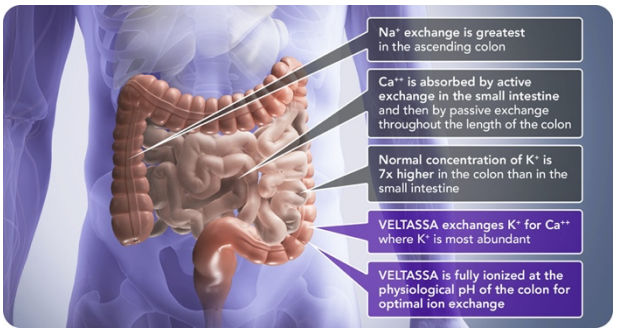



## Loop Diuretics

- Loop diuretics increase $K^+$ loss in the urine in patients with mild-moderate renal impairment; however, diuretics should not be used as monotherapy for removing $K^+$ in patients with hyperkalemic emergency since most studies have consistently demonstrated reduced efficacy in renally impaired patients with persistent hyperkalemia.
- Dose in euvolemic patients: Furosemide 40 mg IV Q12H or a continuous furosemide infusion (2 mg/hour) with an NS infusion to maintain sodium delivery and flow to the kidneys.
- Dose in hypervolemic patients with preserved kidney function: Furosemide 40 mg IV Q12H or a continuous furosemide infusion (2 mg/hour) without NS infusion.
- Severe hyperkalemia in patients with severe renal dysfunction (i.e., kidney failure) are treated with hemodialysis (renal replacement therapy = RRT).

## Gastrointestinal (GI) Cation Exchangers




- GI cation exchangers bind $K^+$ in the GI tract in exchange for other cations (sodium, calcium).
- Patiromer (Veltassa) and sodium zirconium cyclosilicate (Lokelma) are newer agents, preferred over sodium polystyrene (Kayexalate) for safety concerns.
  - Sodium polystyrene (SPS) has been associated colonic necrosis, especially in post-operative patients and patient with bowel obstruction and ileus.
- Patiromer (Veltassa) is a nonabsorbable organic polymer which binds to $K^+$ in the colon in exchange for calcium.
  - Patiromer is not indicated for urgent treatment of hyperkalemia due to its delayed onset of action of 7 hours.
  - Patiromer dose: 8.4 gm PO daily as needed for chronic hyperkalemia.
  - Since patiromer also binds to magnesium in the colon, it may cause hypomagnesemia; therefore, monitor serum magnesium and supplement $Mg^{2+}$ if hypomagnesemia occurs.
- Zirconium cyclosilicate (Lokelma) is a nonabsorbable compound that exchanges both $Na^+$ and $H^+$ ions for $K^+$ throughout the intestinal tract, with an onset of action of 1 hour.
  - Zirconium dose: 10 gm PO TID for 48 hours reduces serum $K^+$ by 0.7 mEq/L in 4 hours.
- SE's of GI Cation Exchangers: constipation, diarrhea, nausea, abdominal distress, and flatulence.

**Key Characteristics of Old and New K+-Binding Agents**

| | Sodium polystyrene sulfonate | Patiromer | Sodium zirconium cyclosilicate |
|---|---|---|---|
| MOA1 | Nonspecific cation binding in exchange for sodium | A polymer exchange resin | Selective $K^+$ binding in exchange for sodium and hydrogen |
| Time to normokalemia | Unconfirmed | Within 1 week[2] | Median 2.2hours<br>Within 24 hours for 84% patients[3] |
| Onset of action | Unknown<br>(generally hours to days) | 7 hours after first dose[4] | 1 hour following the first dose[3] |
| Drug–drug interactions | With antacids, laxatives, digitalis, sorbitol, lithium, and thyroxine[5] | FDA: Must be taken 3 hours apart from other oral drugs[6] | Should be given 2 hours apart from oral medication with gastric pH-dependent bioavailability[7] |
| Location of K+ binding | Colon | Predominantly distal colon | Likely entire GI tract |
| Safety/tolerability | Associated with:<br>• Safety and tolerability concerns[8]<br>• Electrolyte disturbances | • Hypomagnesaemia[9]<br>• GI side effects, e.g. mild-to-moderate constipation | • Mild-to-moderate GI effects[10]<br>• Edema |

1.Garimella PS, et al. Am J Kidney Dis 2016;67:545–547; 2. Weir MR, et al. N Engl J Med 2015;372:211–221; 3. Kosiborod M, et al. JAMA 2014;312:2223–2233; 4. Bushinsky DA, et al. Kidney Int 2015;88:1427–1433; Sanofi-Aventis. Kayexalate Prescribing information 2009; 6. Patiromer Prescribing Information 2016; 7 AstraZeneca. Sodium Zirconium Cyclosilicate Summary of Product Characteristics 2018;; 8. Lepage L, et al. Clin J Am Soc Nephrol 2015;10:2136–2142; 9. Bakris GL, et al. JAMA 2015;314:151–161; 10. Packham DK, et al. N Engl J Med 2015;372:222–231

## Renal Replacement Therapy (Hemodialysis, Peritoneal Dialysis)

- Renal replacement therapy (RRT) is reserved for patients who are severely hyperkalemic ($K > 6.5$), hypervolemic with severe AKI, and nonresponsive to diuretics. RRT is also indicated for patients with refractory acidosis ($pH < 7.1$) and patients with uremic complications (i.e., encephalopathy, pericarditis, seizures).

# Summary: Treatment of Hyperkalemia in Acute Kidney Injury (AKI)

**Emergent/Stabilizing Therapy**

| Modality | Mechanism of Action | Onset | Duration | Prescription | $K^+$ Removed From Body |
|---|---|---|---|---|---|
| Calcium | Antagonizes cardiac conduction abnormalities | 0–5 minutes | 1 hour | Calcium gluconate 10%, 5–30 mL intravenously; or calcium chloride 5%, 5–30 mL intravenously | None |
| Bicarbonate | Distributes $K^+$ into cells | 15–30 minutes | 1–2 hours | $NaHCO_3$, 50–100 mEq intravenously<br>**Note:** Sodium bicarbonate may not be effective in end-stage kidney disease patients; dialysis is more expedient and effective. Some patients may not tolerate the additional sodium load of bicarbonate therapy. | None |
| Insulin | Distributes $K^+$ into cells | 15–60 minutes | 4–6 hours | Regular insulin, 5–10 units intravenously, plus glucose 50%, 25 g intravenously | None |
| Albuterol | Distributes $K^+$ into cells | 15–30 minutes | 2–4 hours | Nebulized albuterol, 10–20 mg in 4 mL normal saline, inhaled over 10 minutes<br>**Note:** Much higher doses are necessary for hyperkalemia therapy (10–20 mg) than for airway disease (2.5 mg). | None |

**Nonemergent/Excretory Therapy**

| Modality | Mechanism of Action | Onset of Action | Prescription | $K^+$ Removed From Body |
|---|---|---|---|---|
| Loop diuretic | Renal $K^+$ excretion | 0.5–2 hours | Furosemide, 40–160 mg intravenously | Variable |
| Patiromer | $Ca^{2+}$-$K^+$ cation exchange resin | ~7 hours | Oral: 4.2–16.8 g once or twice daily | Mean 0.75 mEq/L |
| Sodium circonium cyclosilicate | Selective potassium cation trapping agent | 1 hour | Oral: 10 g up to three times daily | 0.7 mEq/L per 10g dose |
| Sodium polystyrene sulfonate (eg, Kayexalate) | Ion-exchange resin binds $K^+$ | 1–3 hours | Oral: 15–60 g in 20% sorbitol (60–240 mL)<br>Rectal: 30–60 g in 20% sorbitol<br>**Note:** Resins with sorbitol may cause bowel necrosis and intestinal perforation, especially in patients with abnormal bowel function. | 0.5–1 mEq/g resin |
| Hemodialysis[1] | Extracorporeal $K^+$ removal | 1–8 hours | **Note:** A fast and effective therapy for hyperkalemia, hemodialysis can be delayed by vascular access placement and equipment and/or staffing availability. Serum K can be rapidly corrected within minutes, but post-dialysis rebound can occur. | 25–50 mEq/h |
| Peritoneal dialysis | Peritoneal $K^+$ removal | 1–4 hours | Frequent exchanges | 200–300 mEq |

[1]Can be both acute immediate and urgent treatment of hyperkalemia.

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## Hyperkalemia management: Rapid overview of emergency management

| |
|---|
| **Clinical features** |
| Signs and symptoms are uncommon and tend to occur only when serum potassium is >7.0 meq/L; can include muscle weakness and ventricular arrhythmias. |
| There are two major mechanisms of hyperkalemia: |
| Increased potassium release from cells (eg, severe hyperglycemia, rhabdomyolysis). |
| Reduced potassium excretion in urine (eg, hypoaldosteronism, renal failure). |
| Pseudohyperkalemia is a common cause of a reported elevation in serum potassium and must be excluded. It does not reflect true hyperkalemia and does not produce ECG changes. |
| **ECG manifestations** |
| The relationship between the degree of serum potassium elevation and ECG changes varies from patient to patient, and changes are more common with acute-onset hyperkalemia. |
| ECG findings that are commonly observed with more severe elevation of the serum potassium include: |
| Tall peaked T waves. |
| Shrinking and then loss of P waves. |
| Widening of the QRS interval and then "sine wave," ventricular arrhythmia, and asystole. |
| **Early management** |
| Exclude pseudohyperkalemia. |
| Obtain ECG and place patients with hyperkalemic emergency on continuous cardiac monitoring.<br>Patients with hyperkalemic emergency include: |
| Those with clinical manifestations or ECG changes. |
| Those with serum potassium of >6.5 meq/L. |
| Those with serum potassium of >5.5 meq/L plus renal impairment and ongoing tissue breakdown or potassium absorption. |
| In patients with a hyperkalemic emergency: |
| Give **calcium gluconate** 1000 mg (10 mL of 10% solution) IV over two to three minutes. |
| Give **insulin and glucose** (only give glucose if serum glucose is <250 mg/dL [13.9 mmol/L]). A common regimen consists of a bolus injection of 10 units of regular insulin, followed immediately by 50 mL of 50% dextrose (25 g of glucose). We subsequently infuse 10% dextrose at 50 to 75 mL/hour and closely monitor blood glucose levels every hour for five to six hours. |
| Give therapy to remove potassium from the body (refer below). |
| **Remove potassium from the body** |
| Hemodialysis should be performed in patients with ESRD or severe renal impairment. |
| Diuretics (in hypervolemic patients) or saline infusion with IV diuretics can be administered (eg, 40 mg of furosemide every 12 hours) to nonoliguric patients without severe renal impairment. |
| A gastrointestinal cation exchanger (eg, patiromer, 8.4 g orally) can be given, especially in patients with severe renal impairment in whom hemodialysis cannot be swiftly performed. Sodium polystyrene sulfonate (15 to 30 g orally) **should not** be given unless there are no other options to effectively remove potassium from the body in a timely fashion. |

**Treatment of hyperkalemia**

| |
|---|
| **Antagonism of membrane actions of potassium** |
| Calcium |
| **Drive extracellular potassium into the cells** |
| Insulin and glucose |
| Sodium bicarbonate, primarily if metabolic acidosis |
| Beta-2-adrenergic agonists |
| **Removal of potassium from the body** |
| Loop or thiazide diuretics |
| Cation exchange resin |
| Dialysis, preferably hemodialysis if severe |

## Overview of the risk stratification and initial management of patients presenting with hyperkalemia