**TABLE 63-5 CAUSES OF HYPERKALEMIA**

I. Pseudohyperkalemia
  A. Cellular efflux; thrombocytosis, erythrocytosis, leukocytosis, in vitro hemolysis
  B. Hereditary defects in red cell membrane transport
II. Intra- to extracellular shift
  A. Acidosis
  B. Hyperosmolality; radiocontrast, hypertonic dextrose, mannitol
  C. $\beta_2$-Adrenergic antagonists (noncardioselective agents)
  D. Digoxin and related glycosides (yellow oleander, foxglove, bufadienolide)
  E. Hyperkalemic periodic paralysis
  F. Lysine, arginine, and ε-aminocaproic acid (structurally similar, positively charged)
  G. Succinylcholine; thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization
  H. Rapid tumor lysis
III. Inadequate excretion
  A. Inhibition of the renin-angiotensin-aldosterone axis; ↑ risk of hyperkalemia when used in combination
    1. Angiotensin-converting enzyme (ACE) inhibitors
    2. Renin inhibitors; aliskiren (in combination with ACE inhibitors or angiotensin receptor blockers [ARBs])
    3. Angiotensin receptor blockers (ARBs)
    4. Blockade of the mineralocorticoid receptor: spironolactone, eplerenone, drospirenone
    5. Blockade of the epithelial sodium channel (ENaC): amiloride, triamterene, trimethoprim, pentamidine, nafamostat
  B. Decreased distal delivery
    1. Congestive heart failure
    2. Volume depletion
  C. Hyporeninemic hypoaldosteronism
    1. Tubulointerstitial diseases: systemic lupus erythematosus (SLE), sickle cell anemia, obstructive uropathy
    2. Diabetes, diabetic nephropathy
    3. Drugs: nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX2) inhibitors, β-blockers, cyclosporine, tacrolimus
    4. Chronic kidney disease, advanced age
    5. Pseudohypoaldosteronism type II: defects in WNK1 or WNK4 kinases, Kelch-like 3 (KLHL3), or Cullin 3 (CUL3)
  D. Renal resistance to mineralocorticoid
    1. Tubulointerstitial diseases: SLE, amyloidosis, sickle cell anemia, obstructive uropathy, post–acute tubular necrosis
    2. Hereditary: pseudohypoaldosteronism type I; defects in the mineralocorticoid receptor *or* the epithelial sodium channel (ENaC)
  E. Advanced renal insufficiency
    1. Chronic kidney disease
    2. End-stage renal disease
    3. Acute oliguric kidney injury
  F. Primary adrenal insufficiency
    1. Autoimmune: Addison's disease, polyglandular endocrinopathy
    2. Infectious: HIV, cytomegalovirus, tuberculosis, disseminated fungal infection
    3. Infiltrative: amyloidosis, malignancy, metastatic cancer
    4. Drug-associated: heparin, low-molecular-weight heparin
    5. Hereditary: adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, aldosterone synthase deficiency
    6. Adrenal hemorrhage or infarction, including in antiphospholipid syndrome

**Pseudohyperkalemia** Hyperkalemia should be distinguished from factitious hyperkalemia or "pseudohyperkalemia," an artifactual increase in serum $K^+$ due to the release of $K^+$ during or after venipuncture. Pseudohyperkalemia can occur in the setting of excessive muscle activity during venipuncture (e.g., fist clenching), a marked increase in cellular elements (thrombocytosis, leukocytosis, and/or erythrocytosis) with in vitro efflux of $K^+$, and acute anxiety during venipuncture with respiratory alkalosis and redistributive hyperkalemia. Cooling of blood following venipuncture is another cause, due to reduced cellular uptake; the converse is the increased uptake of $K^+$ by cells at high ambient temperatures, leading to normal values for hyperkalemic patients and/or to spurious hypokalemia in normokalemic patients. Finally, there are multiple genetic subtypes of hereditary pseudohyperkalemia, caused by increases in the passive $K^+$ permeability of erythrocytes. For example, causative mutations have been described in the red cell anion exchanger (AE1, encoded by the *SLC4A1* gene), leading to reduced red cell anion transport, hemolytic anemia, the acquisition of a novel AE1-mediated $K^+$ leak, and pseudohyperkalemia.

**Redistribution and Hyperkalemia** Several different mechanisms can induce an efflux of intracellular $K^+$ and hyperkalemia. Acidemia is associated with cellular uptake of $H^+$ and an associated efflux of $K^+$; it is thought that this effective $K^+$-$H^+$ exchange serves to help maintain extracellular pH. Notably, this effect of acidosis is limited to non–anion gap causes of metabolic acidosis and, to a lesser extent, respiratory causes of acidosis; hyperkalemia due to an acidosis-induced shift of potassium from the cells into the ECF does *not* occur in the anion gap acidoses lactic acidosis and ketoacidosis. Hyperkalemia due to hypertonic mannitol, hypertonic saline, and intravenous immune globulin is generally attributed to a "solvent drag" effect, as water moves out of cells along the osmotic gradient. Diabetics are also prone to osmotic hyperkalemia in response to intravenous hypertonic glucose, when given without adequate insulin. Cationic amino acids, specifically lysine, arginine, and the structurally related drug epsilon-aminocaproic acid, cause efflux of $K^+$ and hyperkalemia, through an effective cation-$K^+$ exchange of unknown identity and mechanism. Digoxin inhibits $Na^+/K^+$-ATPase and impairs the uptake of $K^+$ by