Disorders of Potassium Metabolism

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Potassium, the most abundant cation in the human body, regulates intracellular enzyme function and neuromuscular tissue excitability. Serum potassium is normally maintained within the narrow range of 3.5 to 5.5 mEq/L. The intracellular-extracellular potassium ratio (K_i/K_e) largely determines neuromuscular tissue excitability [1]. Because only a small portion of potassium is extracellular, neuromuscular tissue excitability is markedly affected by small changes in extracellular potassium. Thus, the body has developed elaborate regulatory mechanisms to maintain potassium homeostasis. Because dietary potassium intake is sporadic and it cannot be rapidly excreted renally, short-term potassium homeostasis occurs via transcellular potassium shifts [2]. Ultimately, long-term maintenance of potassium balance depends on renal excretion of ingested potassium. The illustrations in this chapter review normal transcellular potassium homeostasis as well as mechanisms of renal potassium excretion.

With an understanding of normal potassium balance, disorders of potassium metabolism can be grouped into those that are due to altered intake, altered excretion, and abnormal transcellular distribution. The diagnostic algorithms that follow allow the reader to limit the potential causes of hyperkalemia and hypokalemia and to reach a diagnosis as efficiently as possible. Finally, clinical manifestations of disorders of potassium metabolism are reviewed, and treatment algorithms for hypokalemia and hyperkalemia are offered.

Recently, the molecular defects responsible for a variety of diseases associated with disordered potassium metabolism have been discovered [3–8]. Hypokalemia and Liddle's syndrome [3] and hyperkalemia and pseudohypoaldosteronism type I [4] result from mutations at different sites on the epithelial sodium channel in the distal tubules. The hypokalemia of Bartter's syndrome can be accounted for by two separate ion transporter defects in the thick ascending limb of Henle's loop [5]. Gitelman's syndrome, a clinical variant of Bartter's

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syndrome, is caused by a mutation in an ion cotransporter in a completely different segment of the renal tubule [6]. The genetic mutations responsible for hypokalemia in the syndrome of apparent mineralocorticoid excess [7] and glucocorticoid-remediable aldosteronism [8] have recently been elucidated and are illustrated below.

Overview of Potassium Physiology

PHYSIOLOGY OF POTASSIUM BALANCE: DISTRIBUTION OF POTASSIUM

ECF 350 mEq (10%)	ICF 3150 mEq (90%)
Plasma 15 mEq (0.4%)	Muscle 2650 mEq (76%)
Interstitial fluid 35 mEq (1%)	Liver 250 mEq (7%)
Bone 300 mEq (8.6%)	Erythrocytes 250 mEq (7%)
$[K^+]$ = 3.5–5.0 mEq/L	$[K^+]$ = 140–150 mEq/L
Urine 90–95 mEq/d	Urine 90–95 mEq/d
Stool 5–10mEq/d	Stool 5–10mEq/d
Sweat < 5 mEq/d	Sweat < 5 mEq/d

FIGURE 3-1

External balance and distribution of potassium. The usual Western diet contains approximately 100 mEq of potassium per day. Under normal circumstances, renal excretion accounts for approximately 90% of daily potassium elimination, the remainder being excreted in stool and (a negligible amount) in sweat. About 90% of total body potassium is located in the intracellular fluid (ICF), the majority in muscle. Although the extracellular fluid (ECF) contains about 10% of total body potassium, less than 1% is located in the plasma [9]. Thus, disorders of potassium metabolism can be classified as those that are due 1) to altered intake, 2) to altered elimination, or 3) to deranged transcellular potassium shifts.

FACTORS CAUSING TRANSCELLULAR POTASSIUM SHIFTS

Factor	Δ Plasma K^+
Acid-base status	
Metabolic acidosis	
Hyperchloremic acidosis	↑↑
Organic acidosis	↔
Respiratory acidosis	↑
Metabolic alkalosis	↓
Respiratory alkalosis	↓
Pancreatic hormones	
Insulin	↓↓
Glucagon	↑
Catecholamines	
β-Adrenergic	↓
α-Adrenergic	↑
Hyperosmolarity	↑
Aldosterone	↓, ↔
Exercise	↑

FIGURE 3-2

Factors that cause transcellular potassium shifts.

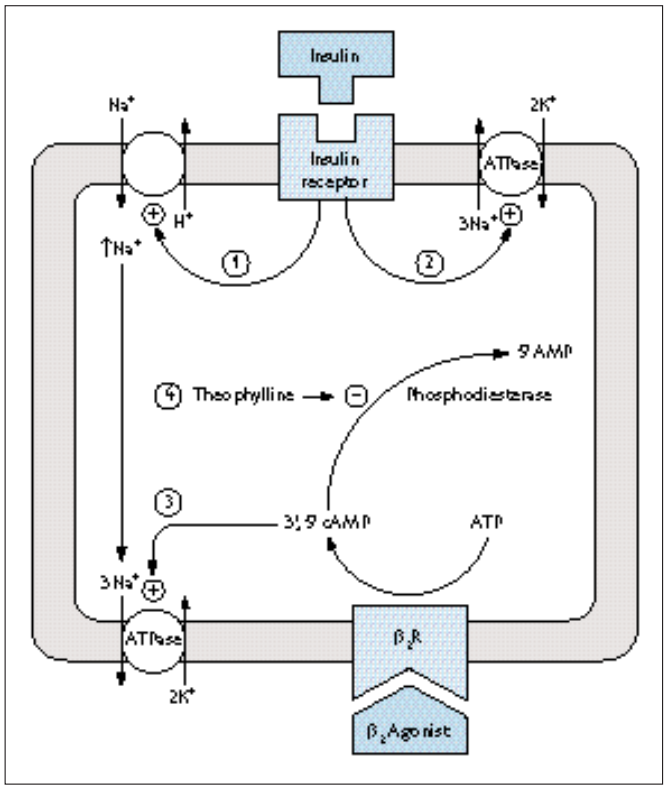

FIGURE 3-3

Extrarenal potassium homeostasis: insulin and catecholamines. Schematic representation of the cellular mechanisms by which insulin and β-adrenergic stimulation promote potassium uptake by extrarenal tissues. Insulin binding to its receptor results in hyperpolarization of cell membranes (1), which facilitates potassium uptake. After binding to its receptor, insulin also activates Na^+-K^+-ATPase pumps, resulting in cellular uptake of potassium (2). The second messenger that mediates this effect has not yet been identified. Catecholamines stimulate cellular potassium uptake via the β_2 adrenergic receptor (β_2R). The generation of cyclic adenosine monophosphate (3′, 5′ cAMP) activates Na^+-K^+-ATPase pumps (3), causing an influx of potassium in exchange for sodium [10]. By inhibiting the degradation of cyclic AMP, theophylline potentiates catecholamine-stimulated potassium uptake, resulting in hypokalemia (4).

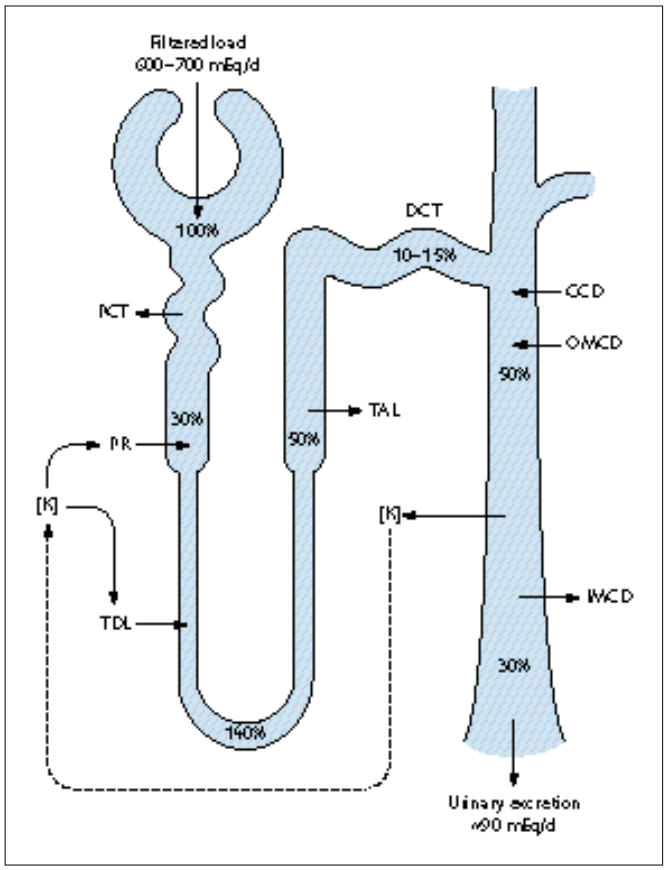

FIGURE 3-4

Renal potassium handling. More than half of filtered potassium is passively reabsorbed by the end of the proximal convolted tubule (PCT). Potassium is then added to tubular fluid in the descending limb of Henle's loop (see below). The major site of active potassium reabsorption is the thick ascending limb of the loop of Henle (TAL), so that, by the end of the distal convoluted tubule (DCT), only 10% to 15% of filtered potassium remains in the tubule lumen. Potassium is secreted mainly by the principal cells of the cortical collecting duct (CCD) and outer medullary collecting duct (OMCD). Potassium reabsorption occurs via the intercalated cells of the medullary collecting duct (MCD). Urinary potassium represents the difference between potassium secreted and potassium reabsorbed [11]. During states of total body potassium depletion, potassium reabsorption is enhanced. Reabsorbed potassium initially enters the medullary interstitium, but then it is secreted into the pars recta (PR) and descending limb of the loop of Henle (TDL). The physiologic role of medullary potassium recycling may be to minimize potassium "backleak" out of the collecting tubule lumen or to enhance renal potassium secretion during states of excess total body potassium [12]. The percentage of filtered potassium remaining in the tubule lumen is indicated in the corresponding nephron segment.

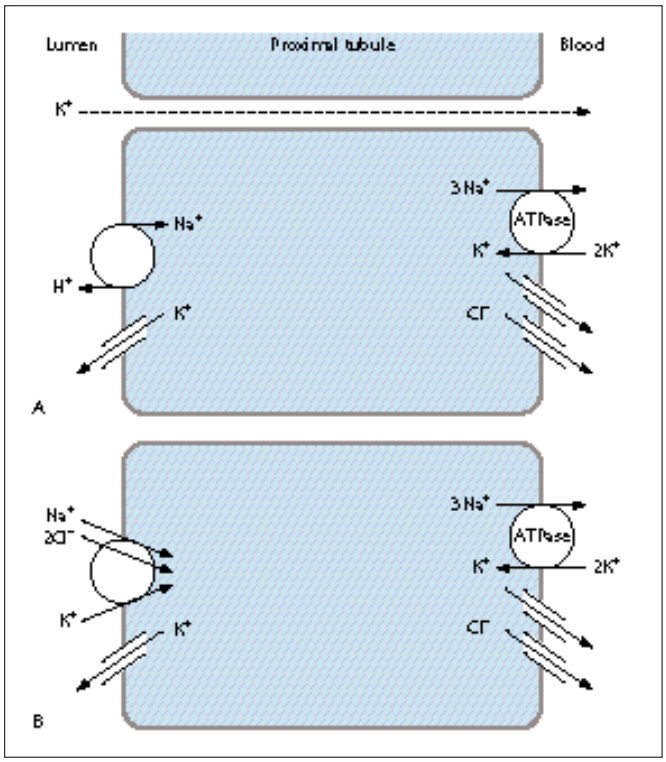

FIGURE 3-5

Cellular mechanisms of renal potassium transport: proximal tubule and thick ascending limb. **A**, Proximal tubule potassium reabsorption is closely coupled to proximal sodium and water transport. Potassium is reabsorbed through both paracellular and cellular pathways. Proximal apical potassium channels are normally almost completely closed. The lumen of the proximal tubule is negative in the early proximal tubule and positive in late proximal tubule segments. Potassium transport is not specifically regulated in this portion of the nephron, but net potassium reabsorption is closely coupled to sodium and water reabsorption. **B**, In the thick ascending limb of Henle's loop, potassium reabsorption proceeds by electroneutral Na^+-K^+-$2Cl^-$ cotransport in the thick ascending limb, the low intracellular sodium and chloride concentrations providing the driving force for transport. In addition, the positive lumen potential allows some portion of luminal potassium to be reabsorbed via paracellular pathways [11]. The apical potassium channel allows potassium recycling and provides substrate to the apical Na^+-K^+-$2Cl^-$ cotransporter [12]. Loop diuretics act by competing for the Cl^- site on this carrier.

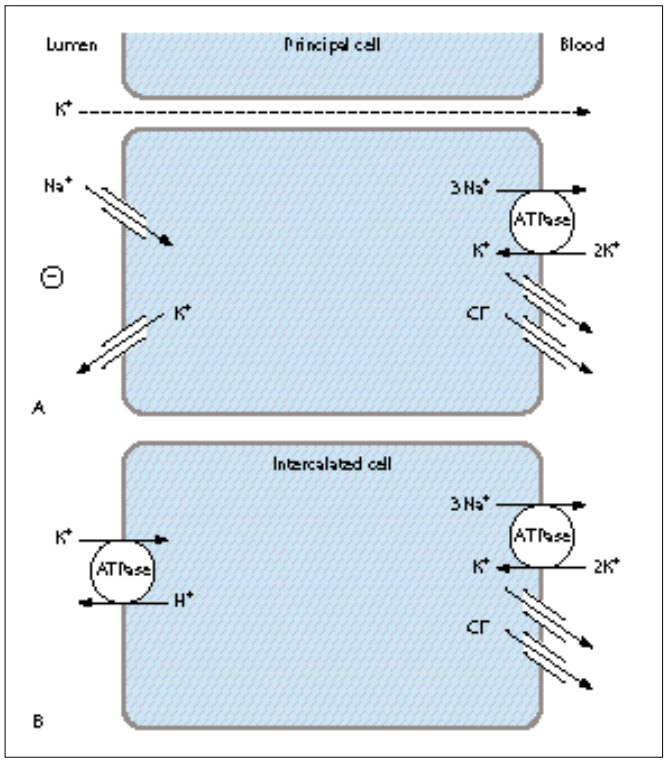

FIGURE 3-6

Cellular mechanisms of renal potassium transport: cortical collecting tubule. **A**, Principal cells of the cortical collecting duct: apical sodium channels play a key role in potassium secretion by increasing the intracellular sodium available to Na^+-K^+-ATPase pumps and by creating a favorable electrical potential for potassium secretion. Basolateral Na^+-K^+-ATPase creates a favorable concentration gradient for passive diffusion of potassium from cell to lumen through potassium-selective channels. **B**, Intercalated cells. Under conditions of potassium depletion, the cortical collecting duct becomes a site for net potassium reabsorption. The H^+-K^+-ATPase pump is regulated by potassium intake. Decreases in total body potassium increase pump activity, resulting in enhanced potassium reabsorption. This pump may be partly responsible for the maintenance of metabolic alkalosis in conditions of potassium depletion [11].

Hypokalemia: Diagnostic Approach

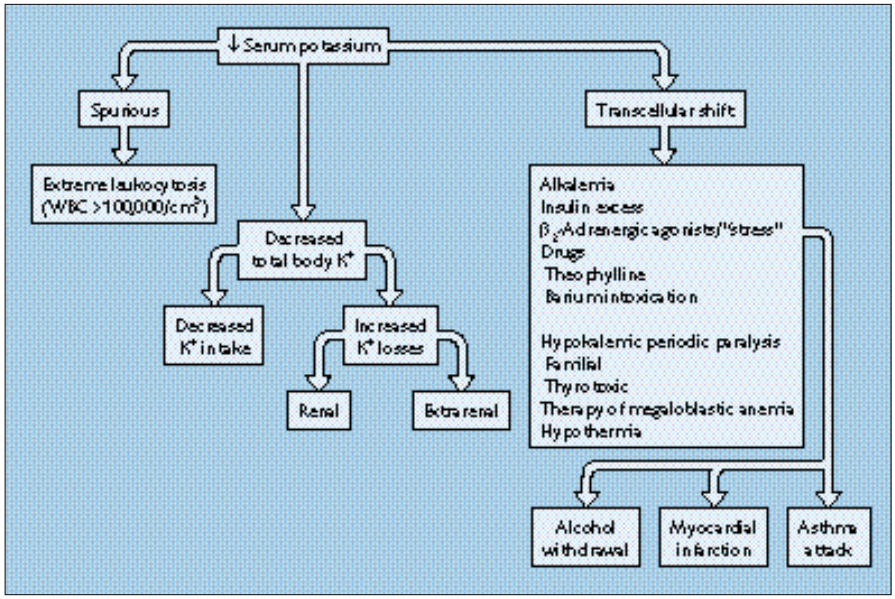

FIGURE 3-7

Overview of diagnostic approach to hypokalemia: hypokalemia without total body potassium depletion. Hypokalemia can result from transcellular shifts of potassium into cells without total body potassium depletion or from decreases in total body potassium. Perhaps the most dramatic examples occur in catecholamine excess states, as after administration of $\beta_2$adreneric receptor (β_2AR) agonists or during "stress." It is important to note that, during some conditions (*eg*, ketoacidosis), transcellular shifts and potassium depletion exist simultaneously. Spurious hypokalemia results when blood specimens from leukemia patients are allowed to stand at room temperature; this results in leukocyte uptake of potassium from serum and artifactual hypokalemia. Patients with spurious hypokalemia do not have clinical manifestations of hypokalemia, as their in vivo serum potassium values are normal. Theophylline poisoning prevents cAMP breakdown (*see* Fig. 3-3). Barium poisoning from the ingestion of soluble barium salts results in severe hypokalemia by blocking channels for exit of potassium from cells. Episodes of hypokalemic periodic paralysis can be precipitated by rest after exercise, carbohydrate meal, stress, or administration of insulin. Hypokalemic periodic paralysis can be inherited as an autosomal-dominant disease or acquired by patients with thyrotoxicosis, especially Chinese males. Therapy of megaloblastic anemia is associated with potassium uptake by newly formed cells, which is occasionally of sufficient magnitude to cause hypokalemia [13].

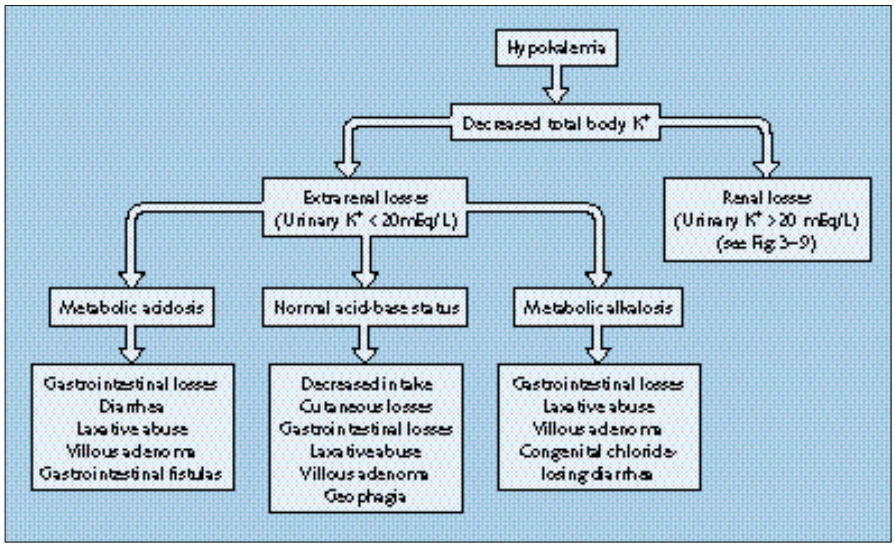

FIGURE 3-8

Diagnostic approach to hypokalemia: hypokalemia with total body potassium depletion secondary to extrarenal losses. In the absence of redistribution, measurement of urinary potassium is helpful in determining whether hypokalemia is due to renal or to extrarenal potassium losses. The normal kidney responds to several (3 to 5) days of potassium depletion with appropriate renal potassium conservation. In the absence of severe polyuria, a "spot" urinary potassium concentration of less than 20 mEq/L indicates renal potassium conservation. In certain circumstances (*eg*, diuretics abuse), renal potassium losses may not be evident once the stimulus for renal potassium wasting is removed. In this circumstance, urinary potassium concentrations may be deceptively low despite renal potassium losses. Hypokalemia due to colonic villous adenoma or laxative abuse may be associated with metabolic acidosis, alkalosis, or no acid-base disturbance. Stool has a relatively high potassium content, and fecal potassium losses could exceed 100 mEq per day with severe diarrhea. Habitual ingestion of clay (pica), encountered in some parts of the rural southeastern United States, can result in potassium depletion by binding potassium in the gut, much as a cation exchange resin does. Inadequate dietary intake of potassium, like that associated ith anorexia or a "tea and toast" diet, can lead to hypokalemia, owing to delayed renal conservation of potassium; however, progressive potassium depletion does not occur unless intake is well below 15 mEq of potassium per day.

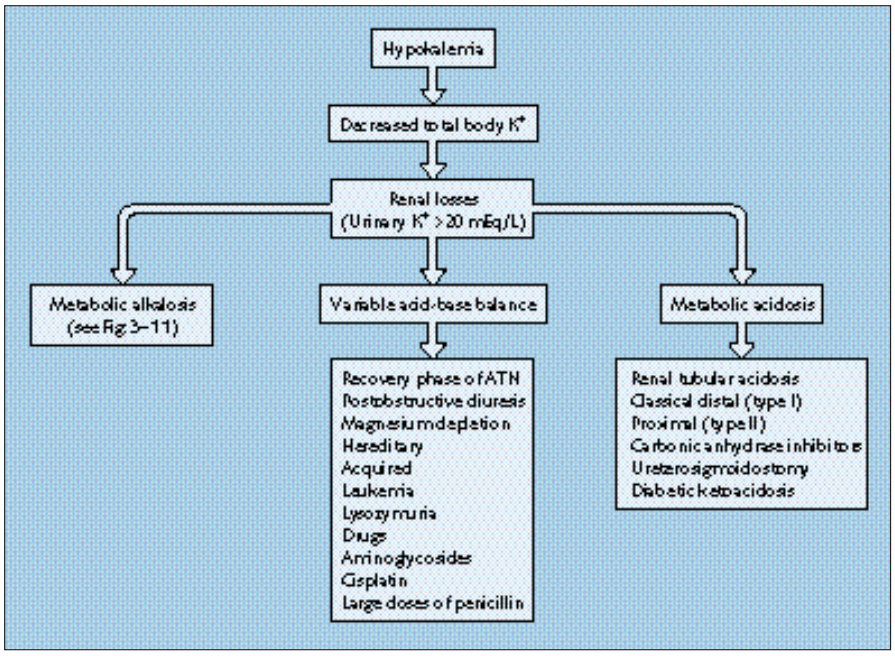

FIGURE 3-9

Diagnostic approach to hypokalemia: hypokalemia due to renal losses with normal acid-base status or metabolic acidosis. Hypokalemia is occasionally observed during the diuretic recovery phase of acute tubular necrosis (ATN) or after relief of acute obstructive uropathy, presumably secondary to increased delivery of sodium and water to the distal nephrons. Patients with acute monocytic and myelomonocytic leukemias occasionally excrete large amounts of lysozyme in their urine. Lysozyme appears to have a direct kaliuretic effect on the kidneys (by an undefined mechanism). Penicillin in large doses acts as a poorly reabsorbable anion, resulting in obligate renal potassium wasting. Mechanisms for renal potassium wasting associated with aminoglycosides and cisplatin are ill-defined. Hypokalemia in type I renal tubular acidosis is due in part to secondary hyperaldosteronism, whereas type II renal tubular acidosis can result in a defect in potassium reabsorption in the proximal nephrons. Carbonic anhydrase inhibitors result in an acquired form of renal tubular acidosis. Ureterosigmoidostomy results in hypokalemia in 10% to 35% of patients, owing to the sigmoid colon's capacity for net potassium secretion. The osmotic diuresis associated with diabetic ketoacidosis results in potassium depletion, although patients may initially present with a normal serum potassium value, owing to altered transcellular potassium distribution.

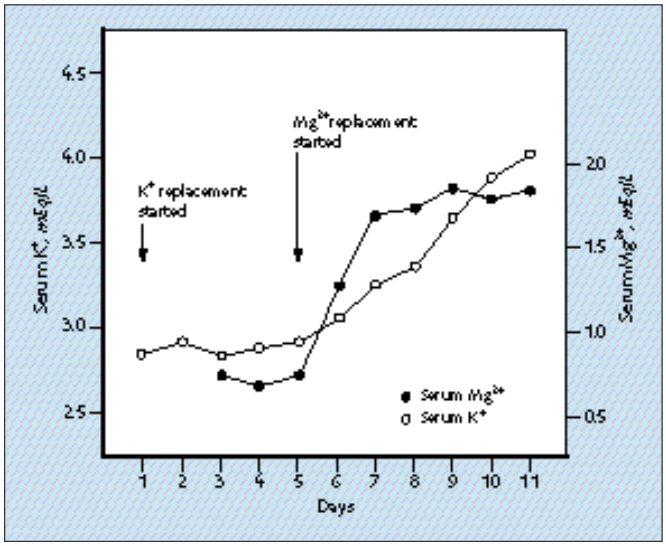

FIGURE 3-10

Hypokalemia and magnesium depletion. Hypokalemia and magnesium depletion can occur concurrently in a variety of clinical settings, including diuretic therapy, ketoacidosis, aminoglycoside therapy, and prolonged osmotic diuresis (as with poorly controlled diabetes mellitus). Hypokalemia is also a common finding in patients with congenital magnesium-losing kidney disease. The patient depicted was treated with cisplatin 2 months before presentation. Attempts at oral and intravenous potassium replacement of up to 80 mEq/day were unsuccessful in correcting the hypokalemia. Once serum magnesium was corrected, however, serum potassium quickly normalized [14].

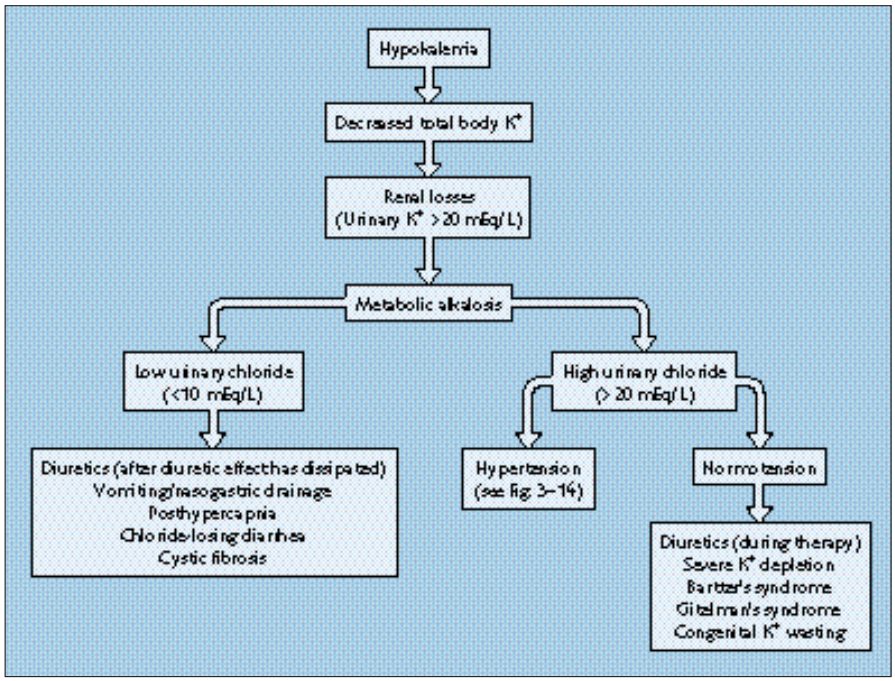

FIGURE 3-11

Diagnostic approach to hypokalemia: hypokalemia due to renal losses with metabolic alkalosis. The urine chloride value is helpful in distinguishing the causes of hypokalemia. Diuretics are a common cause of hypokalemia; however, after discontinuing diuretics, urinary potassium and chloride may be appropriately low. Urine diuretic screens are warranted for patients suspected of surreptious diuretic abuse. Vomiting results in chloride and sodium depletion, hyperaldosteronism, and renal potassium wasting. Posthypercapnic states are often associated with chloride depletion (from diuretics) and sodium avidity. If hypercapnia is corrected without replacing chloride, patients develop chloride-depletion alkalosis and hypokalemia.

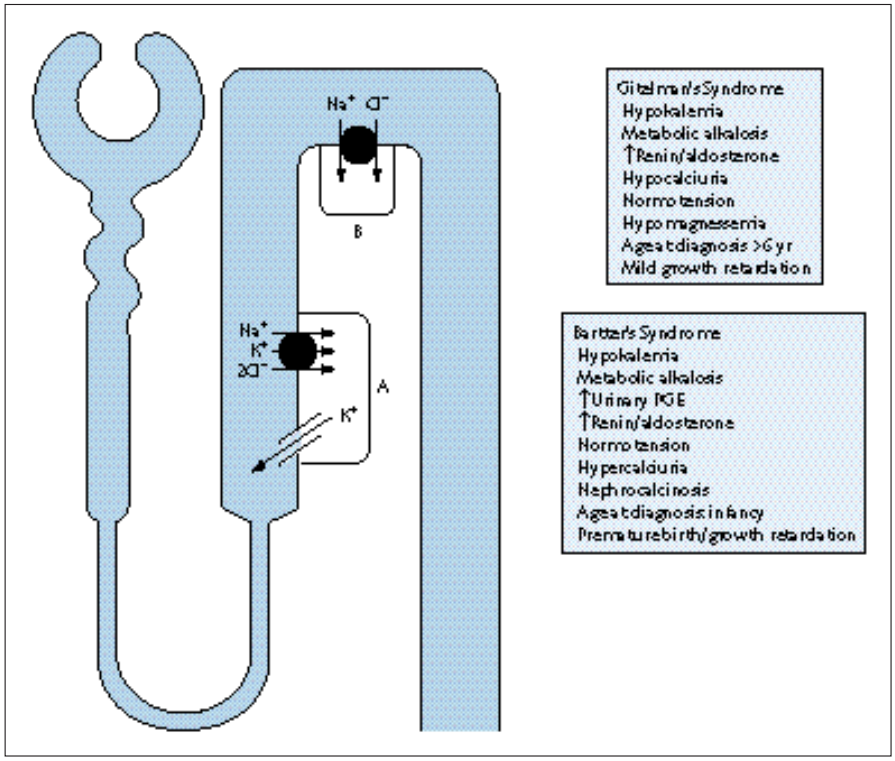

FIGURE 3-12

Mechanisms of hypokalemia in Bartter's syndrome and Gitelman's syndrome. **A**, A defective Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb (TAL) of Henle's loop can account for virtually all features of Bartter's syndrome. Since approximately 30% of filtered sodium is reabsorbed by this segment of the nephron, defective sodium reabsorption results in salt wasting and elevated renin and aldosterone levels. The hyperaldosteronism and increased distal sodium delivery account for the characteristic hypokalemic metabolic alkalosis. Moreover, impaired sodium reabsorption in the TAL results in the hypercalciuria seen in these patients, as approximately 25% of filtered calcium is reabsorbed in this segment in a process coupled to sodium reabsorption. Since potassium levels in the TAL are much lower than levels of sodium or chloride, luminal potassium concentrations are rate limiting for Na^+-K^+-$2Cl^-$ co-transporter activity. Defects in ATP-sensitive potassium channels would be predicted to alter potassium recycling and diminish Na^+-K^+-$2Cl^-$ cotransporter activity. Recently, mutations in the gene that encodes for the Na^+-K^+-$2Cl^-$ cotransporter and the ATP-sensitive potassium channel have been described in kindreds with Bartter's syndrome. Because loop diuretics interfere with the Na^+-K^+-$2Cl^-$ cotransporter, surrepititious diuretic abusers have a clinical presentation that is virtually indistinguishable from that of Bartter's syndrome. **B**, Gitelman's syndrome, which typically presents later in life and is associated with hypomagnesemia and hypocalciuria, is due to a defect in the gene encoding for the thiazide-sensitive Na^+-Cl^- cotransporter. The mild volume depletion results in more avid sodium and calcium reabsorption by the proximal nephrons.

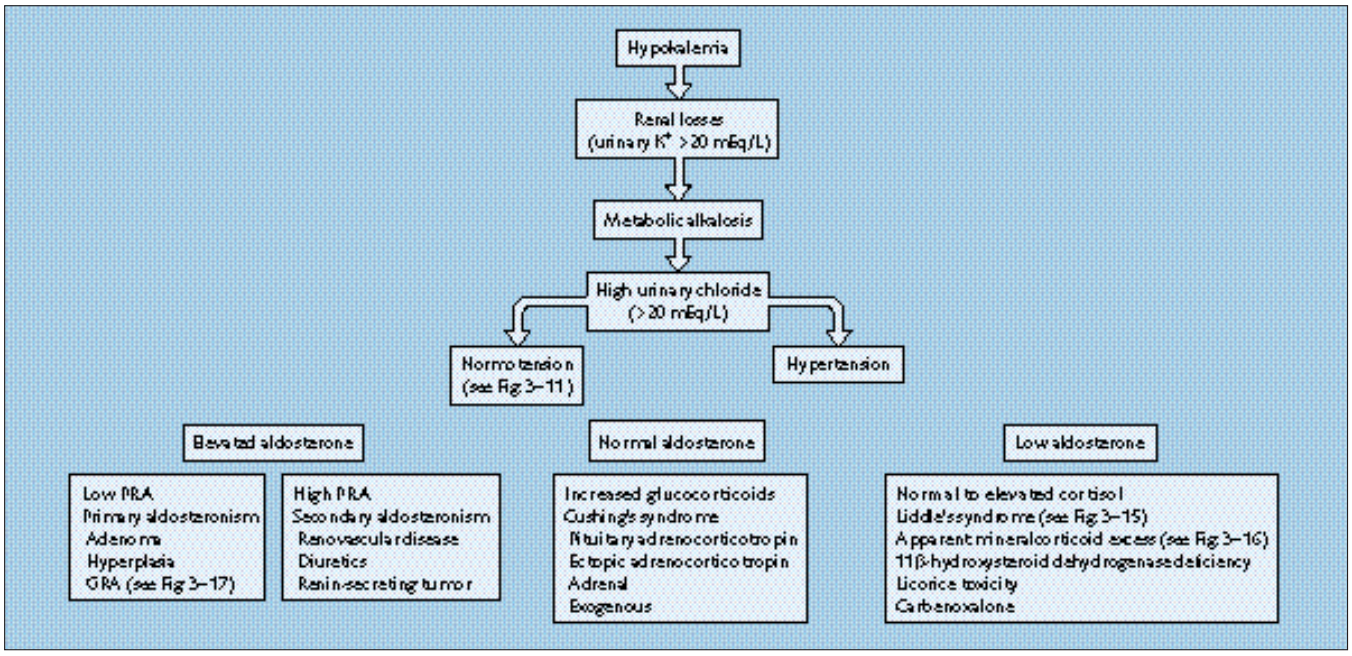

FIGURE 3-13

Diagnostic approach to hypokalemia: hypokalemia due to renal losses with hypertension and metabolic alkalosis.

CHARACTERISTICS OF HYPOKALEMIA WITH HYPERTENSION AND METABOLIC ALKALOSIS

	Aldosterone	Renin	Response to Dexamethasone
Primary aldosteronism	↑	↓	—
11 β-hydroxysteroid dehydrogenase deficiency	↓	↓	+
Glucocorticoid remediable aldosteronism	↑	↓	+
Liddle's syndrome	↓→	↓	—

FIGURE 3-14

Distinguishing characteristics of hypokalemia associated with hypertension and metabolic alkalosis.

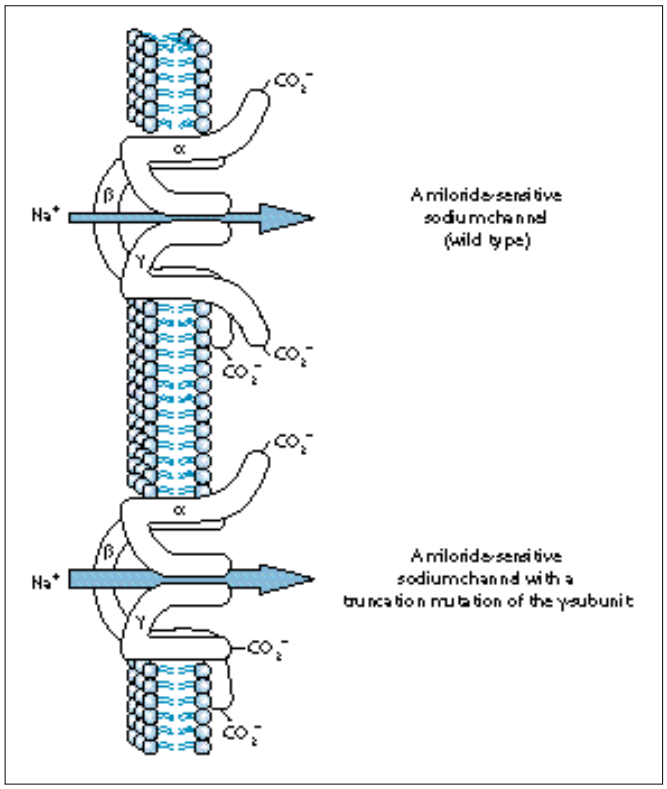

FIGURE 3-15

Mechanism of hypokalemia in Liddle's syndrome. The amiloride-sensitive sodium channel on the apical membrane of the distal tubule consists of homologous α, β, and γ subunits. Each subunit is composed of two transmembrane-spanning domains, an extracellular loop, and intracellular amino and carboxyl terminals. Truncation mutations of either the β or γ subunit carboxyl terminal result in greatly increased sodium conductance, which creates a favorable electrochemical gradient for potassium secretion. Although patients with Liddle's syndrome are not universally hypokalemic, they may exhibit severe potassium wasting with thiazide diuretics. The hypokalemia, hypertension, and metabolic alkalosis that typify Liddle's syndrome can be corrected with amiloride or triamterene or restriction of sodium.

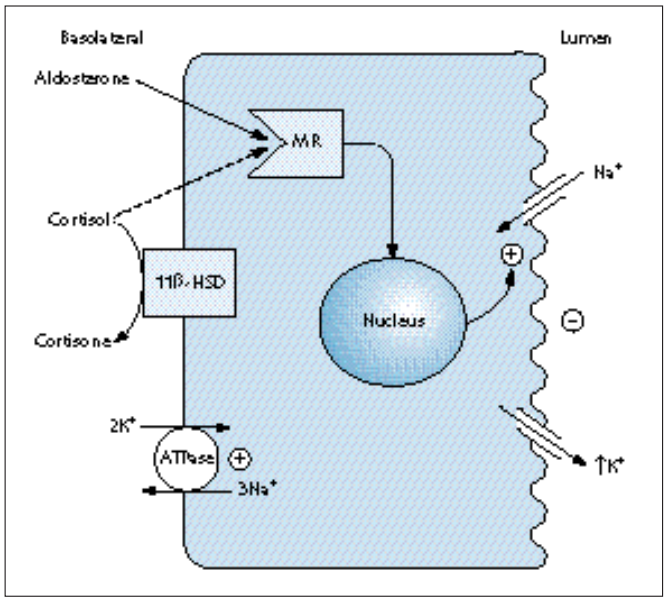

FIGURE 3-16

Mechanism of hypokalemia in the syndrome of apparent mineralocorticoid excess (AME). Cortisol and aldosterone have equal affinity for the intracellular mineralocorticoid receptor (MR); however, in aldosterone-sensitive tissues such as the kidney, the enzyme 11 β-hydroxysteroid dehydrogenase (11 β-HSD) converts cortisol to cortisone. Since cortisone has a low affinity for the MR, the enzyme 11 β-HSD serves to protect the kidney from the effects of glucocorticoids. In hereditary or acquired AME, 11 β-HSD is defective or is inactiveted (by licorice or carbenoxalone). Cortisol, which is present at concentrations approximately 1000-fold that of aldosterone, becomes a mineralocorticoid. The hypermineralocorticoid state results in increased transcription of subunits of the sodium channel and the Na^+-K^+-ATPase pump. The favorable electrochemical gradient then favors potassium secretion [7,15].

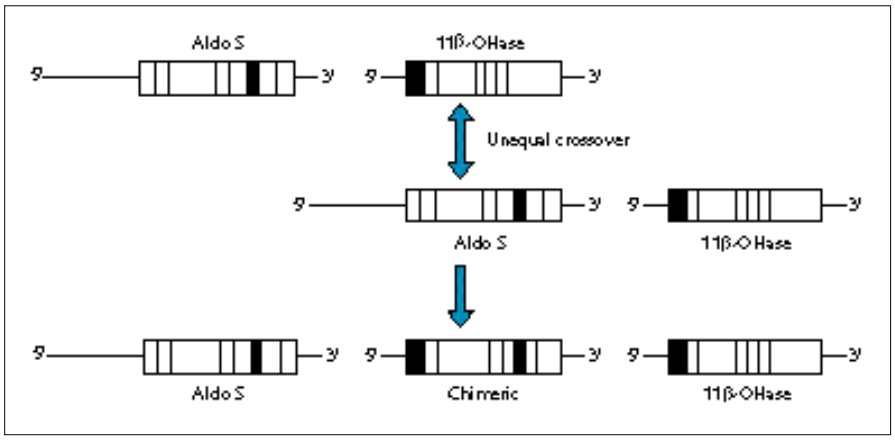

FIGURE 3-17

Genetics of glucocorticoid-remediable aldosteronism (GRA): schematic representation of unequal crossover in GRA. The genes for aldosterone synthase (Aldo S) and 11 β-hydroxylase (11 β-OHase) are normally expressed in separate zones of the adrenal cortex. Aldosterone is produced in the zona glomerulosa and cortisol, in the zona fasciculata. These enzymes have identical intron-extron structures and are closely linked on chromosome 8. If unequal crossover occurs, a new hybrid gene is produced that includes the 5' segment of the 11 β-OHase gene (ACTH-response element and the 11 β-OHase segment) plus the 3' segment of the Aldo S gene (aldosterone synthase segment). The chimeric gene is now under the contol of ACTH, and aldosterone secretion is enhanced, thus causing hypokalemia and hypertension. By inhibiting pituitary release of ACTH, glucocorticoid administration leads to a fall in aldosterone levels and correction of the clinical and biochemical abnormalities of GRA. The presence of Aldo S activity in the zona fasciculata gives rise to characteristic elevations in 18-oxidation products of cortisol (18-hydroxycortisol and 18-oxocortisol), which are diagnostic for GRA [8].

Hypokalemia: Clinical Manifestations

CLINICAL MANIFESTATIONS OF HYPOKALEMIA

- Cardiovascular
  - Abnormal electrocardiogram
  - Predisposition for digitalis toxicity
  - Atrial ventricular arrhythmias
  - Hypertension
- Neuromuscular
  - Smooth muscle
    - Constipation/ileus
    - Bladder dysfunction
  - Skeletal muscle
    - Weakness/cramps
    - Tetany
    - Paralysis
    - Myalgias/rhabdomyolysis
- Renal/electrolyte
  - Functional alterations
    - Decreased glomerular filtration rate
    - Decreased renal blood flow
    - Renal concentrating defect
    - Increased renal ammonia production
    - Chloride wasting
    - Metabolic alkalosis
    - Hypercalciuria
    - Phosphaturia
  - Structural alterations
    - Dilation and vacuolization of proximal tubules
    - Medullary cyst formation
    - Interstitial nephritis
- Endocrine/metabolic
  - Decreased insulin secretion
  - Carbohydrate intolerance
  - Increased renin
  - Decreased aldosterone
  - Altered prostaglandin synthesis
  - Growth retardation

FIGURE 3-18

Clinical manifestations of hypokalemia.

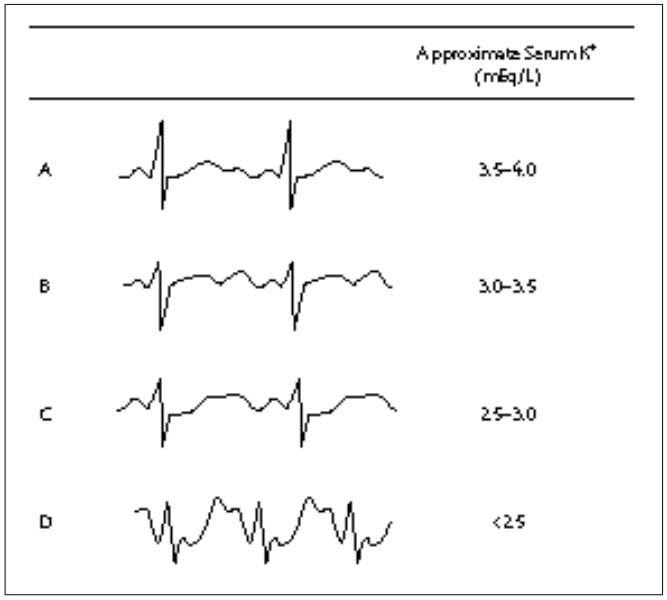

FIGURE 3-19

Electrocardiographic changes associated with hypokalemia. **A**, The U wave may be a normal finding and is not specific for hypokalemia. **B**, When the amplitude of the U wave exceeds that of the T wave, hypokalemia may be present. The QT interval may appear to be prolonged; however, this is often due to mistaking the QU interval for the QT interval, as the latter does not change in duration with hypokalemia. **C**, Sagging of the ST segment, flattening of the T wave, and a prominent U wave are seen with progressive hypokalemia. **D**, The QRS complex may widen slightly, and the PR interval is often prolonged with severe hypokalemia. Hypokalemia promotes the appearance of supraventricular and ventricular ectopic rhythms, especially in patients taking digitalis [16].

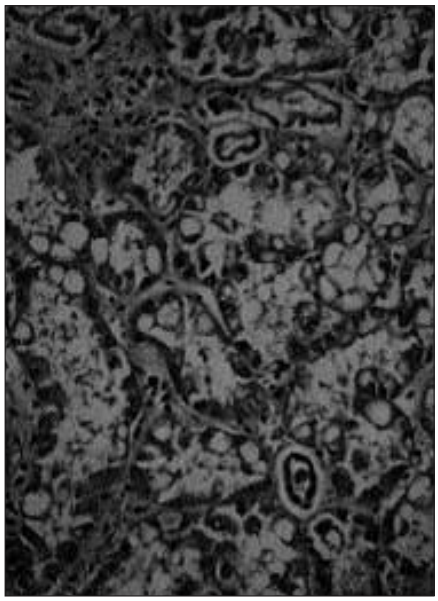

FIGURE 3-20

Renal lesions associated with hypokalemia. The predominant pathologic finding accompanying potassium depletion in humans is vacuolization of the epithelium of the proximal convoluted tubules. The vacoules are large and coarse, and staining for lipids is usually negative. The tubular vacuolation is reversible with sustained correction of the hypokalemia; however, in patients with long-standing hypokalemia, lymphocytic infiltration, interstitial scarring, and tubule atrophy have been described. Increased renal ammonia production may promote complement activation via the alternate pathway and can contribute to the interstitial nephritis [17,18].

Hypokalemia: Treatment

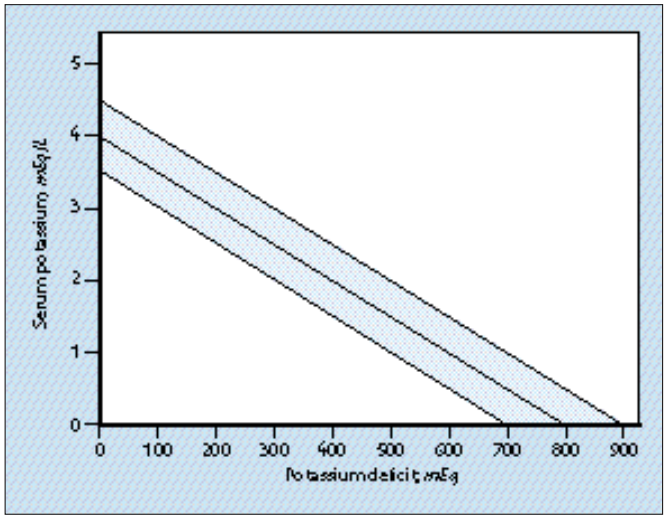

FIGURE 3-21

Treatment of hypokalemia: estimation of potassium deficit. In the absence of stimuli that alter intracellular-extracellular potassium distribution, a decrease in the serum potassium concentration from 3.5 to 3.0 mEq/L corresponds to a 5% reduction (~175 mEq) in total body potassium stores. A decline from 3.0 to 2.0 mEq/L signifies an additional 200 to 400-mEq deficit. Factors such as the rapidity of the fall in serum potassium and the presence or absence of symptoms dictate the aggressiveness of replacement therapy. In general, hypokalemia due to intracellular shifts can be managed by treating the underlying condition (hyperinsulinemia, theophylline intoxication). Hypokalemic periodic paralysis and hypokalemia associated with myocardial infarction (secondary to endogenous β-adrenergic agonist release) are best managed by potassium supplementation [19].

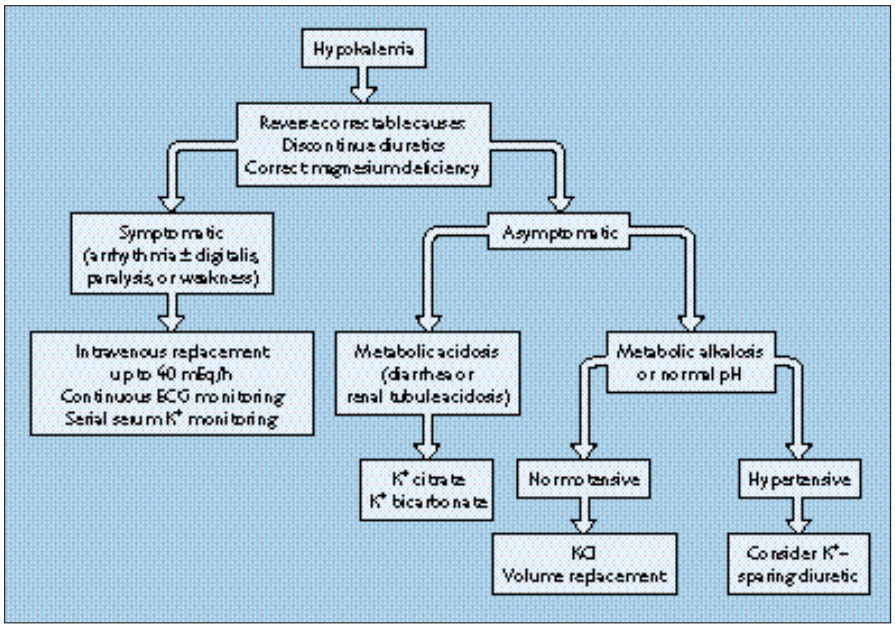

FIGURE 3-22
Treatment of hypokalemia.

Hyperkalemia: Diagnostic Approach

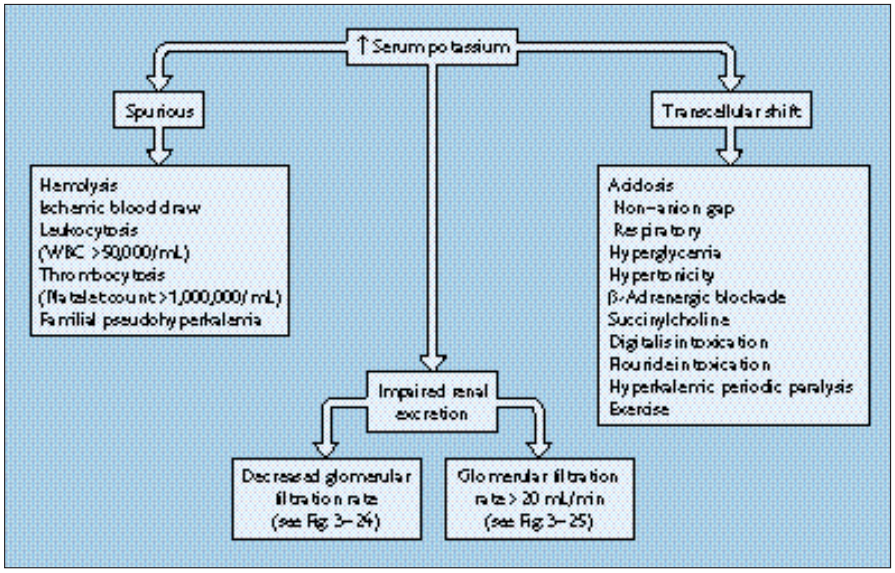

FIGURE 3-23
Approach to hyperkalemia: hyperkalemia without total body potassium excess. Spurious hyperkalemia is suggested by the absence of electrocardiographic (ECG) findings in patients with elevated serum potassium. The most common cause of spurious hyperkalemia is hemolysis, which may be apparent on visual inspection of serum. For patients with extreme leukocytosis or thrombocytosis, potassium levels should be measured in plasma samples that have been promptly separated from the cellular components since extreme elevations in either leukocytes or platelets results in leakage of potassium from these cells. Familial pseudohyperkalemia is a rare condition of increased potassium efflux from red blood cells in vitro. Ischemia due to tight or prolonged tourniquet application or fist clenching increases serum potassium concentrations by as much as 1.0 to 1.6 mEq/L. Hyperkalemia can also result from decreases in K movement into cells or increases in potassium movement from cells. Hyperchloremic metabolic acidosis (in contrast to organic acid, anion-gap metabolic acidosis) causes potassium ions to flow out of cells. Hypertonic states induced by mannitol, hypertonic saline, or poor blood sugar control promote movement of water and potassium out of cells. Depolarizing muscle relaxants such as succinylcholine increase permeability of muscle cells and should be avoided by hyperkalemic patients. The mechanism of hyperkalemia with β-adrenergic blockade is illustrated in Figure 3-3. Digitalis impairs function of the Na^+-K^+-ATPase pumps and blocks entry of potassium into cells. Acute fluoride intoxication can be treated with cation-exchange resins or dialysis, as attempts at shifting potassium back into cells may not be successful.

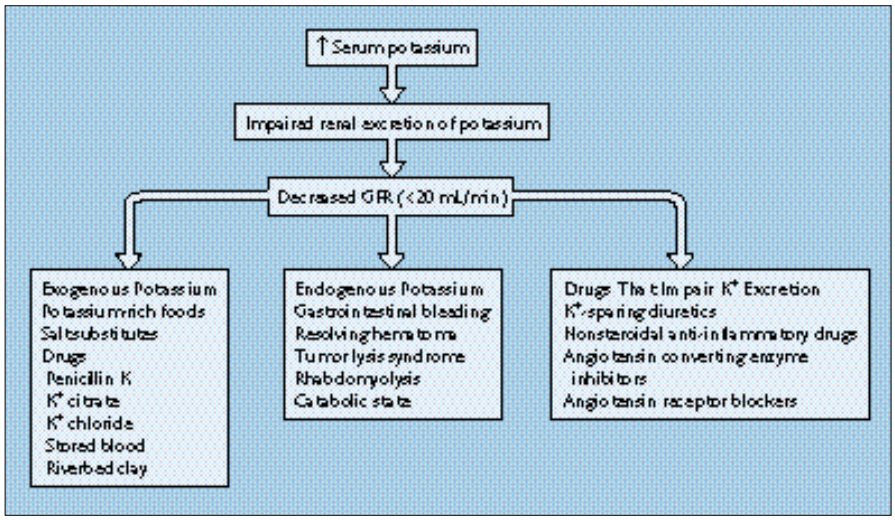

FIGURE 3-24

Approach to hyperkalemia: hyperkalemia with reduced glomerular filtration rate (GFR). Normokalemia can be maintained in patients who consume normal quantities of potassium until GFR decreases to less than 10 mL/min; however, diminished GFR predisposes patients to hyperkalemia from excessive exogenous or endogenous potassium loads. Hidden sources of endogenous and exogenous potassium—and drugs that predispose to hyperkalemia—are listed.

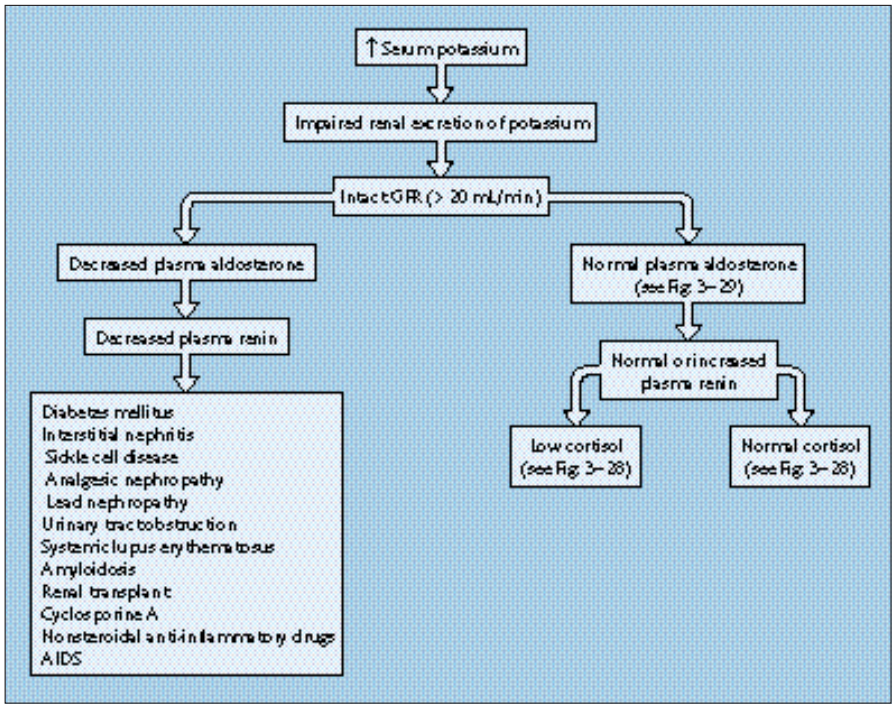

FIGURE 3-25

Approach to hyperkalemia: hyporeninemic hypoaldosteronism. Hyporeninemic hypoaldosteronism accounts for the majority of cases of unexplained hyperkalemia in patients with reduced glomerular filtration rate (GFR) whose level of renal insufficiency is not what would be expected to cause hyperkalemia. Interstitial renal disease is a feature of most of the diseases listed. The transtubular potassium gradient (*see* Fig. 3-26) can be used to distinguish between primary tubule defects and hyporeninemic hypoaldosteronism. Although the transtubular potassium gradient should be low in both disorders, exogenous mineralocorticoid would normalize transtubular potassium gradient in hyporeninemic hypoaldosteronism.

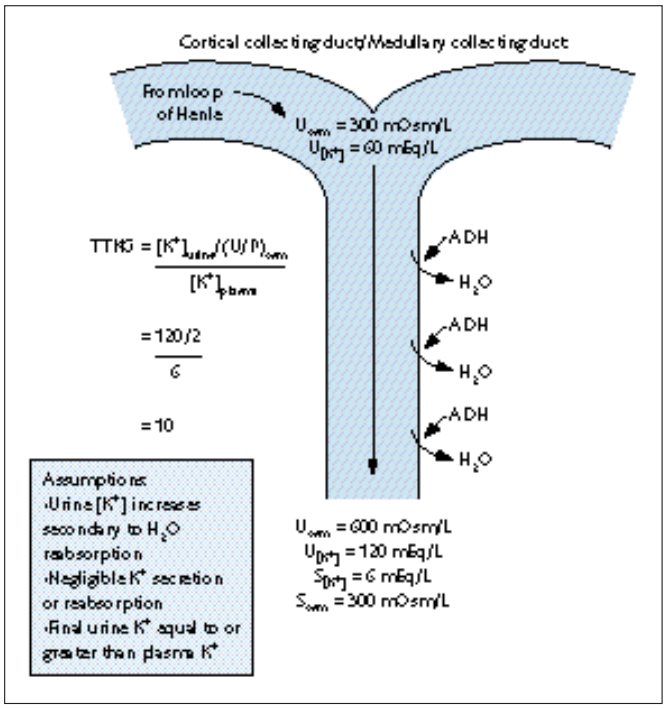

FIGURE 3-26

Physiologic basis of the transtubular potassium concentration gradient (TTKG). Secretion of potassium in the cortical collecting duct and outer medullary collecting duct accounts for the vast majority of potassium excreted in the urine. Potassium secretion in these segments is influenced mainly by aldosterone, plasma potassium concentrations, and the anion composition of the fluid in the lumen. Use of the TTKG assumes that negligible amounts of potassium are secreted or reabsorbed distal to these sites. The final urinary potassium concentration then depends on water reabsorption in the medullary collecting ducts, which results in a rise in the final urinary potassium concentration without addition of significant amounts of potassium to the urine. The TTKG is calculated as follows:

$$TTKG = ([K^+]urine/(U/P)osm)/[K^+]plasma$$

The ratio of $(U/P)_{osm}$ allows for "correction" of the final urinary potassium concentration for the amount of water reabsorbed in the medullary collecting duct. In effect, the TTKG is an index of the gradient of potassium achieved at potassium secretory sites, independent of urine flow rate. The urine must at least be iso-osmolal with respect to serum if the TTKG is to be meaningful [20].

CAUSES FOR HYPERKALEMIA WITH AN INAPPROPRIATELY LOW TTKG THAT IS UNRESPONSIVE TO MINERALOCORTICOID CHALLENGE

- Potassium-sparing diuretics
  - Amiloride
  - Triamterene
  - Spironolactone
- Tubular resistance to aldosterone
  - Interstitial nephritis
  - Sickle cell disease
  - Urinary tract obstruction
  - Pseudohypoaldosteronism type I
- Drugs
  - Trimethoprim
  - Pentamidine
- Increased distal nephron potassium reabsorption
  - Pseudohypoaldosteronism type II
  - Urinary tract obstruction

FIGURE 3-27

Clinical application of the transtubular potassium gradient (TTKG). The TTKG in normal persons varies much but is genarally within the the range of 6 to 12. Hypokalemia from extrarenal causes results in renal potassium conservation and a TTKG less than 2. A higher value suggests renal potassium losses, as through hyperaldosteronism. The expected TTKG during hyperkalemia is greater than 10. An inappropriately low TTKG in a hyperkalemic patient suggests hypoaldosteronism or a renal tubule defect. Administration of the mineralocorticoid 9 α-fludrocortisone (0.05 mg) should cause TTKG to rise above 7 in cases of hypoaldosteronism. Circumstances are listed in which the TTKG would not increase after mineralocorticoid challenge, because of tubular resistance to aldosterone [21].

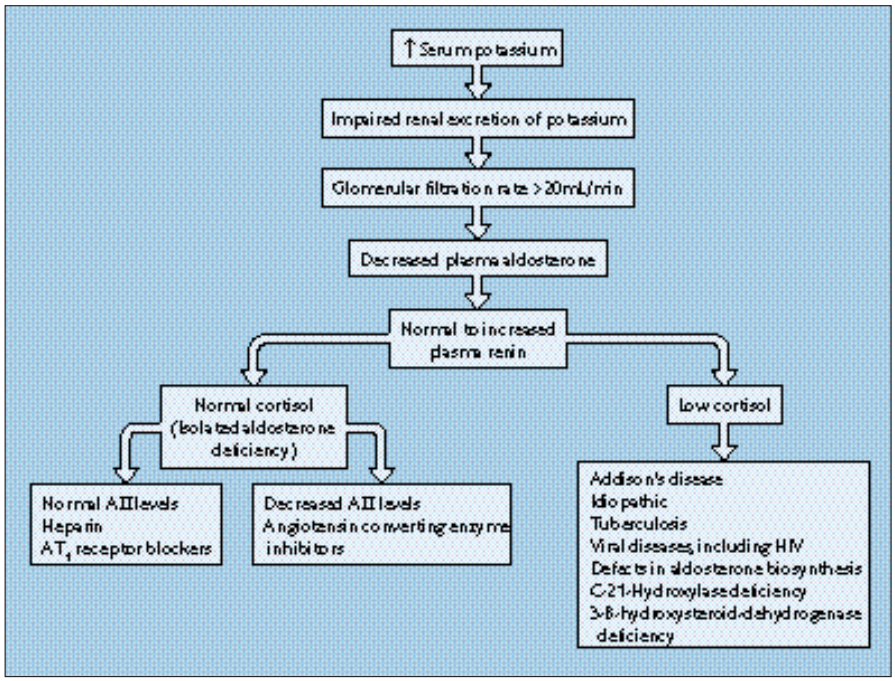

FIGURE 3-28

Approach to hyperkalemia: low aldosterone with normal to increased plasma renin. Heparin impairs aldosterone synthesis by inhibiting the enzyme 18-hydroxylase. Despite its frequent use, heparin is rarely associated with overt hyperkalemia; this suggests that other mechanisms (*eg*, reduced renal potassium secretion) must be present simultaneously for hyperkalemia to manifest itself. Both angiotensin-converting enzyme inhibitors and the angiotensin type 1 receptor blockers (AT_1) receptor blockers interfere with adrenal aldosterone synthesis. Generalized impairment of adrenal cortical function manifested by combined glucocorticoid and mineralocorticoid deficiencies are seen in Addison's disease and in defects of aldosterone biosynthesis.

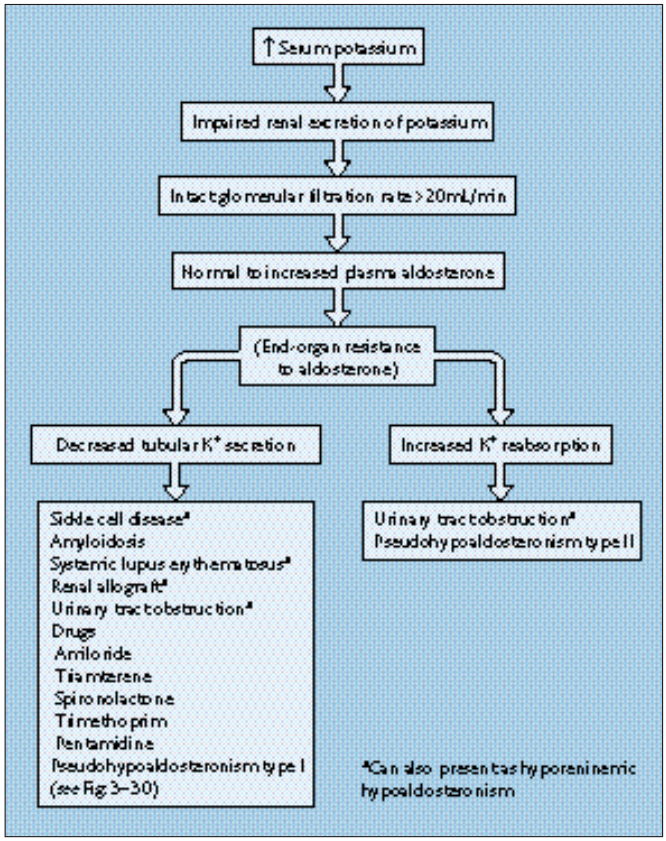

FIGURE 3-29

Approach to hyperkalemia: pseudohypoaldosteronism. The mechanism of decreased potassium excretion is caused either by failure to secrete potassium in the cortical collecting tubule or enhanced reabsorption of potassium in the medullary or papillary collecting tubules. Decreased secretion of potassium in the cortical and medullary collecting duct results from decreases in either apical sodium or potassium channel function or diminished basolateral Na^+-K^+-ATPase activity. Alternatively, potassium may be secreted normally but hyperkalemia can develop because potassium reabsorption is enhanced in the intercalated cells of the medullary collecting duct (*see* Fig. 3-4). The transtubule potassium gradient (TTKG) in both situations is inappropriately low and fails to normalize in response to mineralocorticoid replacement.

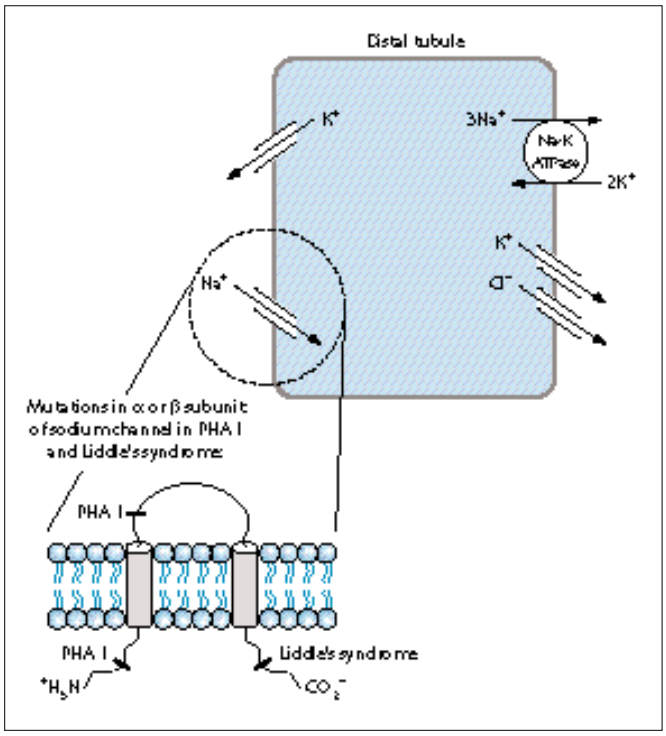

FIGURE 3-30
Mechanism of hyperkalemia in pseudohypoaldosteronism type I (PHA I). This rare autosomally transmitted disease is characterized by neonatal dehydration, failure to thrive, hyponatremia, hyperkalemia, and metabolic acidosis. Kidney and adrenal function are normal, and patients do not respond to exogenous mineralocorticoids. Genetic mutations responsible for PHA I occur in the α and β subunits of the amiloride-sensitive sodium channel of the collecting tubule. Frameshift or premature stop codon mutations in the cytoplasmic amino terminal or extracellular loop of either subunit disrupt the integrity of the sodium channel and result in loss of channel activity. Failure to reabsorb sodium results in volume depletion and activation of the renin-aldosterone axis. Furthermore, since sodium reabsorption is indirectly coupled to potassium and hydrogen ion secretion, hyperkalemia and metabolic acidosis ensue. Interestingly, when mutations are introduced into the cytoplasmic carboxyl terminal, sodium channel activity is increased and Liddle's syndrome is observed [4].

Hyperkalemia: Clinical Manifestations

CLINICAL MANIFESTATIONS OF HYPERKALEMIA

- Cardiac
  - Abnormal electrocardiogram
  - Atrial/ventricular arrhythmias
  - Pacemaker dysfunction
- Neuromuscular
  - Paresthesias
  - Weakness
  - Paralysis
- Renal electrolyte
  - Decreased renal NH_4^+ production
  - Natriuresis
- Endocrine
  - Increased aldosterone secretion
  - Increased insulin secretion

FIGURE 3-31
Clinical manifestations of hyperkalemia.

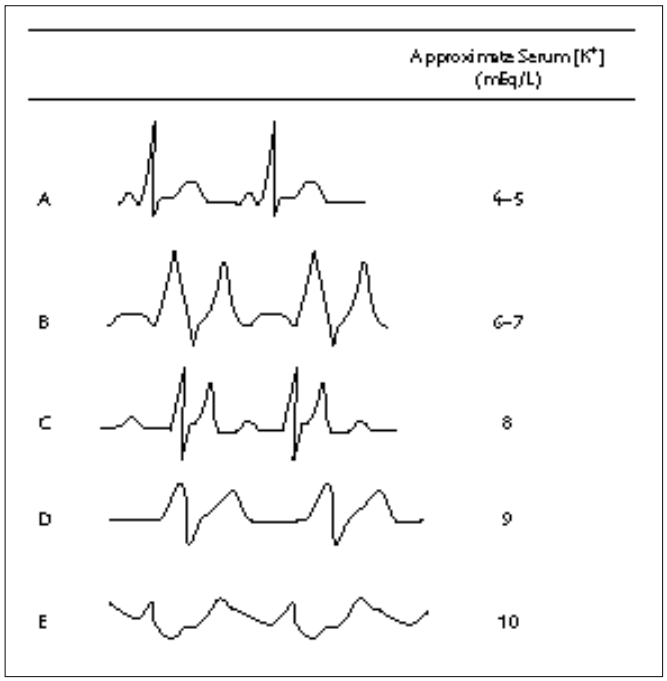

FIGURE 3-32
Electrocardiographic (ECG) changes associated with hyperkalemia. **A**, Normal ECG pattern. **B**, Peaked, narrow-based T waves are the earliest sign of hyperkalemia. **C**, The P wave broadens and the QRS complex widens when the plamsa potassium level is above 7 mEq/L. **D**, With higher elevations in potassium, the P wave becomes difficult to identify. **E**, Eventually, an undulating sinusoidal pattern is evident. Although the ECG changes are depicted here as correlating to the severity of hyperkalemia, patients with even mild ECG changes may abruptly progress to terminal rhythm disturbances. Thus, hyperkalemia with any ECG changes should be treated as an emergency.

Hyperkalemia: Treatment

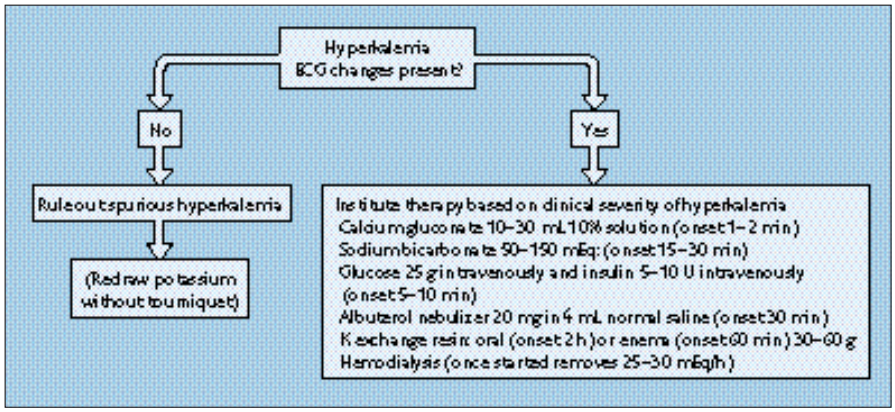

FIGURE 3-33
Treatment of hyperkalemia.

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