serum K^+ level acutely. Treatment with nebulized albuterol (5–20 mg) lowers the serum K^+ level for at least 2 hours.[22,23]

Exchange Resins. Definitive treatment for hyperkalemia remains the removal of K^+ from the body. Exchange resins (e.g., sodium polystyrene sulfonate [Kayexalate]) and hemodialysis are two such options. Given orally or rectally, each gram of Kayexalate can remove approximately 1.0 mEq of K^+. An oral dose of 20 g of Kayexalate in a sorbitol produces effects in 1 to 2 hours. Rectal enemas of 50 g of Kayexalate, retained for 30 minutes, work in approximately 30 minutes. Kayexalate should be used with caution in patients with poor cardiovascular reserve because of the potential to exacerbate volume overload.

Dialysis. Hemodialysis corrects hyperkalemia rapidly, and consultation with a nephrologist is indicated in the unstable hyperkalemic patient with newly diagnosed or chronic renal failure. Hyperkalemia resulting from severe rhabdomyolysis is difficult to treat with the usual measures and also mandates consultation for emergency dialysis. Dialysis removes K^+ from the blood only, and subsequent shifts of intracellular K^+ may cause rebound hyperkalemia. Dialysis can be effective in treating hyperkalemia-induced cardiac arrest.[24]

Underlying Cause. Treatment of any underlying causative disorder should be initiated at the same time as therapy for hyperkalemia. This may include the treatment of rhabdomyolysis with fluids and bicarbonate; treatment of Addison's disease with corticosteroids, IV fluids, and glucose; treatment of digitalis toxicity with digoxin-binding antibodies; or discontinuation of drugs that may have precipitated the hyperkalemia.

Patients with hyperkalemia should be admitted to a monitored bed with care provided by a clinician skilled in the treatment of electrolyte disorders.

CALCIUM

Normal Physiology

Hundreds of enzymatic reactions are mediated by changes in intracellular calcium. Cellular growth and reproduction, membrane integrity, receptor activation, neurotransmission, glandular secretion, enzyme activation, muscle contraction, cardiac contractility, platelet aggregation, and immune function all depend on the precise regulation of free calcium. Evidence also indicates that cellular injury and ultimately cell death are mediated by changes in free intracellular calcium.[25]

The adult human body contains approximately 1200 g of calcium, with more than 99% in the mineral component of bone. The remaining 1% is distributed in three different plasma fractions: (1) approximately 50% is bound to serum proteins, primarily albumin; (2) 10% is complexed with serum anions (phosphate, bicarbonate, citrate, lactate); and (3) 40% is in the free ionized state (Ca^{2+}). Ca^{2+} is the physiologically active form, and concentrations are tightly regulated by the endocrine system.

Dietary calcium is absorbed in the proximal intestine through both active and passive processes. Absorption is enhanced by the action of vitamin D. In the kidneys, 99% of the filtered load of calcium is reabsorbed. Approximately 90% of calcium reabsorption occurs passively in the proximal tubule and loop of Henle. The remaining 10% occurs in the distal tubule under the control of *parathyroid hormone* (PTH, parathormone). A fall in free serum calcium stimulates the release of PTH, which in turn increases reabsorption. PTH also mediates the hydroxylation of vitamin D to its active form, 1,25-dihydroxycholecalciferol (1,25-DHCC).

The skeleton acts as a calcium pool that buffers acute changes in serum concentration. When the serum calcium level falls, PTH stimulates an increase in bone turnover and the release of calcium into the serum. A rise in serum calcium suppresses PTH production and causes the release of calcitonin. *Calcitonin* decreases osteoclastic activity and enhances skeletal deposition of calcium.

The serum calcium level reflects the net outcome of several processes. On one hand, intestinal absorption and bone resorption add calcium to the blood; on the other, calcium is lost from the blood by renal excretion, skeletal uptake, or abnormal deposition in soft tissues. A decrease in the serum Ca^{2+} activates the PTH–vitamin D system to increase the entry of calcium into the blood from the bone and gastrointestinal tract. A rise in the serum calcium level suppresses the PTH–vitamin D system and increases the release of calcitonin, which decreases calcium entry into the blood.

Many hospital laboratories measure total serum calcium concentrations, which is a combination of both Ca^{2+} and calcium that is bound to proteins. Normal value of total serum calcium ranges from 8.5 to 10.5 mg/dL. However, the total serum calcium is often a poor indicator of the Ca^{2+} status, since abnormalities of serum protein concentrations (primarily albumin) affect the total calcium. A decrease in albumin concentration lowers the measured serum calcium, and an increase raises it, even as the Ca^{2+} level remains unchanged. A corrected serum calcium level that accounts for changes in serum albumin concentrations can be calculated as follows:

$$\begin{aligned}\text{Corrected calcium} &= \text{serum calcium (mg/dL)} \\ &\cong +0.8[4 - \text{serum albumin (g/dL)}]\end{aligned}$$

This formula is only an estimate, and the Ca^{2+} should be measured whenever hypocalcemia is suggested. Blood gas analyzers can measure Ca^{2+} from a sample of blood or serum. The normal range is 1.00 to 1.15 mmol/L.

Changes in acid-base status influence the ratio of bound to ionized calcium without altering the total measured calcium. Acidosis decreases calcium binding to albumin, and alkalosis increases binding. Thus, acute changes in blood pH may have important physiologic effects by changing the Ca^{2+} level even when the total serum calcium level remains unchanged.[25]

Hypocalcemia

Principles of Disease

The causes of ionized hypocalcemia are numerous (Box 123-7) and can be divided into disorders causing PTH insufficiency, vitamin D insufficiency, PTH resistance states, and calcium chelation.

Parathyroid Hormone Insufficiency. PTH insufficiency can be caused by either primary or secondary hypoparathyroidism. Primary hypoparathyroidism is rare and is usually congenital. Maternal hyperparathyroidism may result in fetal parathyroid hypoplasia and transient hypoparathyroidism.

Secondary hypoparathyroidism is more common and is most often iatrogenic, resulting from inadvertent removal of the parathyroid glands or disruption of the vascular supply during parathyroid, thyroid, or carotid surgery. Permanent hypocalcemia is the usual consequence. Excision of a functional parathyroid adenoma, leaving only the chronically suppressed but otherwise unaffected parathyroid tissue, causes hypocalcemia that usually resolves over several days. Metastatic carcinoma or infiltrative disorders (e.g., hemochromatosis, sarcoidosis, Wilson's disease) may destroy parathyroid tissue and cause hypocalcemia. Both severe hypomagnesemia and severe hypermagnesemia can impair PTH release. Drugs that may suppress parathyroid function include chemotherapeutic agents, cimetidine, and ethanol.

BOX 123-7 CAUSES OF HYPOCALCEMIA

- Parathyroid hormone insufficiency
  - Primary hypoparathyroidism
    - Congenital syndromes
    - Maternal hyperparathyroidism
  - Secondary hypoparathyroidism
    - Neck surgery
    - Metastatic carcinoma
    - Infiltrative disorders
    - Hypomagnesemia, hypermagnesemia
    - Sepsis
    - Pancreatitis
    - Burns
    - Drugs (chemotherapeutics, ethanol, cimetidine)
- Vitamin D insufficiency
  - Congenital rickets
  - Malnutrition
  - Malabsorption
  - Liver disease
  - Renal disease
    - Acute and chronic renal failure
    - Nephrotic syndrome
  - Hypomagnesemia
  - Sepsis
  - Anticonvulsants (phenytoin, primidone)
- Parathyroid hormone resistance states (pseudohypoparathyroidism)
- Calcium chelation
  - Hyperphosphatemia
  - Citrate
  - Free fatty acids
  - Alkalosis
  - Fluoride poisoning

Vitamin D. Vitamin D deficiency can result in hypocalcemia because of decreased gastrointestinal calcium absorption. Nutritional vitamin D deficiency is rare in the United States because of the fortification of milk but can occur when exposure to sunlight is limited, especially in elderly, chronically ill, and debilitated patients. Children of mothers with vitamin D deficiency may be born with congenital rickets. Characteristic findings include hypocalcemia, hypophosphatemia, and specific radiographic findings (widening of the distal radius and ulna, craniotabes). Vitamin D insufficiency resulting from intestinal malabsorption can occur in patients with small-bowel or biliary disease or pancreatic exocrine failure. Cholestyramine can also prevent adequate vitamin D absorption. Once absorbed, vitamin D is hydroxylated in the liver and kidney to its active form, 1,25-DHCC. Hepatic disease and renal disease may lead to inadequate activation of the vitamin. Hypercatabolism of vitamin D may occur in association with agents that stimulate the hepatic microsomal oxidase system, such as the anticonvulsants phenytoin and primidone.

Parathyroid Hormone Resistance States. PTH resistance states are termed *pseudohypoparathyroidism*. These rare familial syndromes are characterized by renal unresponsiveness to PTH and resultant parathyroid hyperplasia.[26] Differentiation from hypoparathyroidism is based on elevated PTH levels and a lack of increase in urinary cyclic adenosine monophosphate after PTH administration.

Hypocalcemia is common in patients with chronic renal failure. This results from vitamin D deficiency, impaired responsiveness to PTH, and phosphate retention. Generally, these patients are asymptomatic, possibly because of a protective effect of systemic acidosis. However, rapid correction of metabolic acidosis with exogenous sodium bicarbonate can precipitate severe hypocalcemia, often causing tetany and seizures.

Calcium Chelation. Calcium complexes with several different substances in serum, including proteins, fatty acids, and anions. Increases in the concentration of these substances may thus result in ionized hypocalcemia. Citrate is used as a blood preservative and anticoagulant. The citrate load associated with massive blood transfusion (>6 U) causes hypocalcemia in up to 94% of patients.[27] Hypocalcemia is usually short-lived, and Ca^{2+} levels return to normal shortly after transfusion. Because citrate is metabolized by temperature-dependent enzymes in tissues and excreted by the liver, hypothermia and hepatic failure are important risk factors for protracted hypocalcemia after blood transfusion. Citrate is also a constituent of radiocontrast material, and hypocalcemia has been associated with the administration of these agents.

Exogenous administration of phosphate and endogenous hyperphosphatemia (e.g., with acute renal failure, rhabdomyolysis, or tumor lysis syndrome) are well-known causes of hypocalcemia.[28] Exogenous bicarbonate also complexes with calcium and may cause symptomatic hypocalcemia. Alkalosis, either metabolic or respiratory, enhances the binding of calcium to serum proteins, resulting in ionized hypocalcemia. Free fatty acids liberated in various conditions (e.g., acute pancreatitis, hyperadrenergic states, acute ethanol ingestion) can chelate free Ca^{2+} to form calcium soaps. Fluoride poisoning can also cause hypocalcemia. This may occur after exposure to hydrofluoric acid or ammonium bifluoride, components of many household cleaners and rust removers. These compounds release free fluoride ion, a direct cellular toxin that binds Ca^{2+}, forming calcium fluoride. Numerous cases of severe hypocalcemia, cardiac dysrhythmias, and death have been reported after ingestion, inhalation, or cutaneous exposure to these products.

Clinical Features

The clinical manifestations of hypocalcemia depend not only on the serum level but also on the rapidity with which it declines. Although the signs and symptoms of hypocalcemia are numerous (Box 123-8), the effects on neuromuscular function predominate.

A declining serum calcium level is associated with progressive neuromuscular hyperexcitability. CNS manifestations include depression, irritability, confusion, and focal or generalized seizures. Peripheral nervous system manifestations include perioral paresthesias, muscle weakness and cramps, fasciculations, and tetany.[25] Latent tetany can often be demonstrated by eliciting Chvostek's or Trousseau's sign. *Chvostek's sign* is elicited by tapping over the facial nerve and causing twitching of the ipsilateral facial muscles. *Trousseau's sign* describes carpal spasm in response to inflation of an arm blood pressure cuff to 20 mm Hg above systolic blood pressure for 3 minutes.

Severe hypocalcemia causes a decrease in myocardial contractility and, rarely, bradycardia, hypotension, and symptomatic congestive heart failure. Patients with preexisting cardiac dysfunction and those taking digoxin or diuretics are especially at risk. The ECG may demonstrate QT prolongation, and an inverse relationship exists between the serum calcium level and the QT interval. However, the ECG is a poor predictor of hypocalcemia and should not be used to rule in or rule out this disorder.

Bronchospasm and laryngeal spasm occur rarely. Symptoms and signs ranging from anxiety and depression to psychosis and dementia can be seen.

BOX 123-8 CLINICAL FEATURES OF HYPOCALCEMIA

Neuromuscular
Paresthesias
Muscle weakness
Muscle spasm
Tetany
Chvostek's and Trousseau's signs
Hyper-reflexia
Seizures

Cardiovascular
Bradycardia
Hypotension
Cardiac arrest
Digitalis insensitivity
QT prolongation

Pulmonary
Bronchospasm
Laryngeal spasm

Psychiatric
Anxiety
Depression
Irritability
Confusion
Psychosis
Dementia

Management

In patients with suggested hypocalcemia or a documented low total serum calcium level, the first step in management should be verification of true ionized hypocalcemia. When hypocalcemia is the presumed cause of tetany, seizures, hypotension, or dysrhythmias, it may be appropriate to initiate treatment before the Ca^{2+} level is available. All patients with symptomatic hypocalcemia should be treated with parenteral calcium. Two different formulations are readily available in most emergency departments: (1) 10-mL ampules of 10% calcium chloride, which contain 360 mg of elemental calcium, and (2) 10-mL ampules of 10% calcium gluconate, which contain 93 mg of elemental calcium. For the adult patient, the recommended initial dose is 100 to 300 mg of elemental calcium given as calcium chloride or calcium gluconate. This dose of calcium increases the serum Ca^{2+} level for only a short time (1–2 hours) and should be followed by repeated doses or an infusion at a rate of 0.5 to 2 mg/kg/hr.[25] For neonates, infants, and children, the recommended initial dose is 0.5 to 1.0 mL/kg of 10% calcium gluconate over 5 minutes.[26]

The most common side effects of IV calcium administration are hypertension, nausea, vomiting, and flushing. Bradycardia and heart block occur in rare cases. Patients receiving IV calcium should be placed on a cardiac monitor, and administration should be discontinued if bradycardia ensues. Calcium should be administered with extra caution in patients taking digoxin because it may precipitate (or exacerbate) digoxin-induced cardiotoxicity. Because calcium can cause severe tissue irritation and necrosis if it extravasates, it should always be given through a well-functioning catheter. Whenever possible, calcium chloride should be diluted in 5% dextrose in water (D_5W).[25,26]

Symptoms refractory to appropriate doses of calcium may be caused by coexisting hypomagnesemia. In patients with normal renal function, administration of 2 to 4 g of 10% magnesium sulfate should be considered.

Patients with asymptomatic hypocalcemia can be treated with oral calcium supplements. Available preparations include calcium ascorbate, calcium gluconate, and calcium lactate. Most patients require 1 to 4 g of elemental calcium daily in divided doses.

Hypercalcemia

Principles of Disease

Hypercalcemia is a relatively common medical disorder. Routine laboratory screening can be expected to detect hypercalcemia in 0.1 to 1.0% of patients, depending on the population being screened.[29-31] Hypercalcemia is usually mild (<12 mg/dL) and asymptomatic and rarely requires emergency treatment. Nevertheless, hypercalcemia may be an important clue to a serious underlying medical disorder. *Hypercalcemic crisis* occurs in a subset of patients who have severe hypercalcemia (usually >14 mg/dL) and is generally associated with prominent signs and symptoms. In this situation, immediate measures to lower the serum calcium level are indicated.

Although hypercalcemia has many causes, more than 90% of cases result from primary hyperparathyroidism or malignancy (Box 123-9).[32]

Primary hyperparathyroidism is the most common cause of hypercalcemia in outpatients, accounting for 25 to 50% of cases.[33] This can result from parathyroid adenoma (80%), parathyroid hyperplasia (15%), or parathyroid carcinoma (5%).[34] Hyperparathyroidism can also occur in association with other endocrine tumors as part of one of the familial syndromes of

BOX 123-9 CAUSES OF HYPERCALCEMIA

Primary hyperparathyroidism
Malignant disease
  Parathyroid hormone–related protein
  Ectopic production of 1,25-dihydroxyvitamin D
  Other bone-resorbing substances
  Osteolytic bone metastasis
Medications
  Thiazide diuretics
  Lithium
  Estrogens
  Vitamin D toxicity
  Vitamin A toxicity
  Calcium ingestion
Granulomatous disorders
  Sarcoidosis
  Tuberculosis
  Coccidioidomycosis
  Berylliosis
  Histoplasmosis
  Leprosy
Nonparathyroid endocrine disorders
  Hyperthyroidism
  Adrenal insufficiency
  Pheochromocytoma
  Acromegaly
  Vasoactive intestinal polypeptide–producing tumor
Miscellaneous
  Milk-alkali syndrome
  Immobilization
  Idiopathic hypocalcemia of infancy
  Physiologic (in the newborn)

multiple endocrine adenomatosis. In primary hyperparathyroidism, the PTH level is elevated in more than 90% of cases; the remainder of patients have high-normal PTH levels that are inappropriate for the degree of hypercalcemia. An elevated PTH level leads to increased bone resorption, a relative decrease in renal calcium excretion, and increased intestinal calcium absorption. Patients typically develop hypercalcemia, phosphaturia, hypophosphatemia, and a hyperchloremic metabolic acidosis.

Malignancy is the most common cause of hypercalcemia in hospitalized patients, and hypercalcemia is the most common paraneoplastic complication of cancer. The reported prevalence of hypercalcemia in patients with cancer ranges from 15 to 60%.[35,36] A multitude of solid tumors can cause hypercalcemia, including cancers of breast, lung, colon, stomach, cervix, uterus, ovary, kidney, bladder, and head and neck. Hypercalcemia is also seen with hematologic malignancies such as multiple myeloma and lymphoma. Hypercalcemia in patients with cancer can result from several different mechanisms, including production of PTH-related protein by the tumor.[37,38] This polypeptide is homologous to PTH in its first 13 N-terminal amino acids and binds to the PTH receptor, mimicking all the actions of the hormone. PTH-related protein is secreted by solid malignancies and their metastases and is not subject to normal feedback control mechanisms.[39] Assays for PTH-related protein are available to confirm this cause of cancer-related hypercalcemia.[40] Less often, hypercalcemia results from the production of other bone-resorbing substances by the tumor (e.g., transforming growth factor-α) or the local effects of osteolytic skeletal metastasis. Virtually all patients with cancer-associated hypercalcemia have low concentrations of PTH, readily distinguishing this cause of hypercalcemia from primary hyperparathyroidism.

Thiazide diuretics are associated with up to 20% of cases of hypercalcemia. These agents can increase the reabsorption of calcium in the distal convoluted tubule by as much as 70%. Hypercalcemia is typically mild, although it may be exaggerated in patients with dehydration.

Granulomatous disorders (e.g., sarcoidosis, tuberculosis, coccidioidomycosis, histoplasmosis, leprosy) can cause hypercalcemia. In these conditions, activated macrophages convert 1,25-hydroxyvitamin D to its active form (1,25-DHCC), resulting in enhanced intestinal calcium absorption, hypercalcemia, and hypercalciuria.[41] Certain lymphomas cause severe hypercalcemia by a similar mechanism. Interestingly, hypercalcemia in patients with sarcoidosis occurs as a seasonal event in patients who live in the Northern Hemisphere, presumably because of increased production of vitamin D in the skin during longer exposure to the summer sun.[42]

Acute vitamin A intoxication is an uncommon but well-recognized cause of hypercalcemia, resulting from an increase in osteoclastic activity. This usually occurs after an accidental massive ingestion of a preparation containing vitamin A. Chronic hypervitaminosis A can occur in patients using large doses of the vitamin for a variety of dermatologic conditions (e.g., acne vulgaris). Because vitamin A is highly lipophilic, toxicity may take several weeks to resolve after discontinuation of the vitamin. Increased exogenous vitamin D intake may also result in hypercalcemia.

Milk-alkali syndrome is caused by excessive ingestion of calcium and absorbable antacids such as milk or calcium carbonate and is characterized by hypercalcemia, alkalosis, and renal failure. The disorder is less common since nonabsorbable antacids and H_2-receptor antagonists became available for the treatment of peptic ulcer disease.

Lithium therapy for bipolar (manic-depressive) disorders can put patients at increased risk for developing hypercalcemia. Clinical and in vitro studies suggest that lithium alters the release of PTH by shifting the set point for inhibition of hormone secretion by circulating calcium.

Thyroid hormone causes hypercalcemia by increasing bone turnover through direct stimulation of osteoclastic bone resorption. In most cases, the symptoms of hyperthyroidism predominate, and hypercalcemia does not become apparent until hyperthyroidism is managed. Hypercalcemia can also be seen in patients after renal transplantation or in the early phase of acute tubular necrosis.

Clinical Features

The clinical manifestations of hypercalcemia are nonspecific and vary widely from patient to patient (Box 123-10). Severity of symptoms depends on both the level of serum calcium and the rapidity of its rise.

Hypercalcemia decreases neuronal conduction and in general causes CNS depression. Symptoms range from fatigue, weakness, and difficulty concentrating to confusion, lethargy, stupor, and even coma.

Hypercalcemia has several effects on the cardiovascular system. The volume depletion with which hypercalcemia is typically associated can result in hypotension. Because hypercalcemia causes an increase in vascular tone, however, the blood pressure may be misleadingly normal. Characteristic ECG changes include shortening of the QT interval and, to a lesser degree, prolongation of the PR interval and QRS widening. Rarely, severe hypercalcemia causes sinus bradycardia, bundle branch block, high-degree atrioventricular block, and even cardiac arrest. Calcium potentiates the action of digoxin, and the side effects of digoxin are accentuated when hypercalcemia is present.[34]

BOX 123-10 Clinical Features of Hypercalcemia

Neurologic
Fatigue, weakness
Confusion, lethargy
Ataxia
Coma
Hypotonia, diminished deep tendon reflexes

Cardiovascular
Hypertension
Sinus bradycardia, atrioventricular block
ECG abnormalities (short QT, bundle branch block)
Ventricular dysrhythmias
Potentiation of digoxin toxicity

Renal
Polyuria, polydipsia
Dehydration
Loss of electrolyte
Prerenal azotemia
Nephrolithiasis
Nephrocalcinosis

Gastrointestinal
Nausea, vomiting
Anorexia
Peptic ulcer disease
Pancreatitis
Constipation, ileus

ECG, electrocardiographic.

An acute rise in the serum calcium level impairs the reabsorption of fluid and electrolytes in the renal tubule, promoting the development of dehydration, which is worsened by vomiting and poor fluid intake. This may lead to a vicious cycle of volume depletion, reduced GFR and calcium excretion, intensified hypercalcemia, and further dehydration, culminating in oliguric renal failure, coma, and death. Chronically, hypercalcemia and associated volume depletion predispose the patient to renal calculi, nephrocalcinosis, and calcium-induced interstitial nephritis.

Anorexia, nausea, vomiting, and abdominal pain are common but nonspecific symptoms of hypercalcemia. Hypercalcemia decreases smooth muscle tone and may lead to constipation or intestinal ileus. An increased serum calcium level enhances the release of hydrochloric acid, gastrin, and pancreatic enzymes. Chronic hypercalcemia has been associated with an increased risk of peptic ulcer disease and pancreatitis.

Management

Treatment should be initiated at once in patients with evidence of significant dehydration, alteration of consciousness, or symptomatic dysrhythmias. Patients with severe hypercalcemia (>14 mg/dL) require rapid treatment regardless of symptoms. The four basic goals of therapy are (1) restoration of intravascular volume, (2) enhancement of renal calcium elimination, (3) reduction of osteoclastic activity, and (4) treatment of the primary disorder (Box 123-11). Although it may not be realistic to expect to achieve these goals in the emergency department, it is important for the emergency physician to initiate therapy and involve the appropriate consultants as early as possible.

Fluid Administration. The administration of isotonic saline is the first step in the management of severe hypercalcemia. Once the intravascular volume has been restored to normal, the serum calcium level will usually have decreased by 1.6 to 2.4 mg/dL, although hydration alone rarely leads to complete normalization. The expansion of intravascular volume increases renal calcium clearance by increasing GFR and Na^+ delivery to the distal tubules. The rate of fluid administration should be based on the severity of hypercalcemia, the degree of dehydration, and the patient's cardiovascular tolerance of acute volume expansion. In elderly patients and those with poor left ventricular function, central venous pressure monitoring can be used to adjust fluid administration rates. Two to 5 L per day is often required. Coexisting electrolyte deficiencies should also be corrected.

Furosemide. Loop diuretics such as furosemide inhibit the resorption of calcium in the thick ascending loop of Henle, increasing the calciuric effect of hydration. Volume expansion must precede the administration of furosemide, however, because the drug's effect depends on the delivery of calcium to the distal nephron. IV doses of 10 to 40 mg every 6 to 8 hours are usually sufficient. Thiazide diuretics should not be used because they enhance distal absorption of calcium and may worsen hypercalcemia.

Osteoclast Inhibitors. Therapy for severe hypercalcemia should also include agents that reduce the mobilization of calcium from bone. Drugs that inhibit osteoclast-mediated bone resorption include the bisphosphonates, calcitonin, glucocorticoids, and gallium nitrate. Because these drugs are used very infrequently in the emergency department, consultation with a specialist and/or pharmacist to select the best agent and dosing strategy is advised.

The bisphosphonates act by inhibiting osteoclastic bone resorption and decreasing the viability of osteoclasts.[43] Etidronate, palmidronate, and zoledronic acid have similar efficacy and a reasonable adverse effect profile.[44-47]

Calcitonin is a naturally occurring hormone that lowers serum calcium by inhibiting osteoclastic activity. Among the anticalcemic agents available, calcitonin has the most rapid onset of action, although it causes only a modest reduction in the serum calcium level.[48] When hypercalcemia is severe and the need to lower the serum calcium is urgent, it is reasonable to administer a dose of calcitonin in combination with a more potent agent such as a bisphosphonate.

The glucocorticoids act by inhibiting the action of vitamin D. They may be effective calcium-lowering agents in patients with hypercalcemia caused by hematologic malignancies, granulomatous disorders, or vitamin D intoxication.

Underlying Cause. Pharmacologic therapy does not permanently normalize the serum calcium concentration. The underlying cause of the hypercalcemia needs to be treated as well. Primary hyperparathyroidism is definitively managed by parathyroidectomy. In the hands of experienced surgeons, more than 90% of patients are cured. When hypercalcemia is caused by malignancy, treatment must be directed at the underlying tumor because normocalcemia is difficult to sustain without successful treatment of the underlying cause. Hypercalcemia caused by medication responds to discontinuation of the offending agent. Hypercalcemia caused by nonparathyroid endocrine disease responds to treatment of the underlying disorder.

BOX 123-11 MANAGEMENT OF HYPERCALCEMIA

- Restoration of intravascular volume
  - Correct dehydration with isotonic solution
  - Correct associated electrolyte abnormalities
- Enhancement of renal calcium elimination
  - Saline diuresis
  - Loop diuretics (e.g., furosemide)
  - *Avoid* thiazide diuretics
- Reduction of osteoclastic activity
  - (Consult specialist for agent selection dosing.)
  - Bisphosphonates
    - Etidronate
    - Pamidronate
  - Zoledronic acid
  - Calcitonin
  - Hydrocortisone
- Treatment of primary disorder
  - Parathyroidectomy for hyperparathyroidism
  - Withdrawal of causative medications
  - Treatment of nonparathyroid endocrine disorders

MAGNESIUM

Normal Physiology

Magnesium (Mg^{2+}) is the second most abundant intracellular cation. It is a cofactor in hundreds of enzymatic reactions, including all those involving adenosine triphosphate (ATP). Magnesium is essential for the production and use of energy, DNA, and protein synthesis, ion channel gating, hormone receptor binding, neurotransmission, cardiac excitability, and muscle contraction.[49]

The adult human body contains approximately 2000 mEq of magnesium. One half of total magnesium is in the mineral