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Emergency Management of Malignancy-Associated Hypercalcemia

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ABSTRACT
The most common cause of hypercalcemia in the emergency department (ED) is malignancy-associated hypercalcemia (MAH), which can be caused by direct bone resorption from bone metastases, vitamin D secreting malignancies, and increased parathyroid hormone (PTH) or PTH-related protein (PTHrP) levels. Malignancy-associated hypercalcemia is associated with a very poor prognosis, with half of the patients dying within a month of diagnosis. Management consists of adequate hydration, bisphosphonate therapy, and correction of other abnormal electrolyte levels. Currently, no therapies have demonstrated an effect on mortality and are therefore viewed only as a means of stabilizing the patient until the underlying condition can be treated. All MAH patients should receive an oncology consult as soon as possible so they are able to receive treatment for the causative malignancy and increase their chance of survival. **Key words:** bisphosphonate, emergency department, hypercalcemia, malignancy, MAH (malignancy-associated hypercalcemia), pamidronate, zoledronate

HYPERCALCEMIA can be defined as mild, moderate, or severe on the basis of a patient's serum calcium level, with the most common classifications listed in Table 1. Approximately 1% of the total calcium (Ca^{2+}_{total}) in our body resides in the extracellular and intracellular spaces, with the remaining 99% residing in bone. Ionized calcium (Ca^{2+}_{ion}), which is filtered and reabsorbed by the kidneys, compared with protein bound calcium, accounts for about 48% of serum calcium. Although Ca^{2+}_{total} is used more commonly than ionized concentrations to define hypercalcemia, it is the ionized calcium in serum that potentiates the detrimental side effects. Therefore, if hypercalcemia is suspected upon presentation to the emergency department (ED), it is important to determine both the Ca^{2+}_{total} and Ca^{2+}_{ion} concentrations.

Both low albumin and low pH may lead to a normal total serum calcium level that masks an elevated ionized calcium level. Albumin binds both calcium and hydrogen ions. Therefore, in the presence of low albumin, less of the total serum calcium is protein bound, which results in a disproportionate amount of ionized calcium. In addition, in an acidic

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Table 1. Hypercalcemia classifications

	Total serum calcium (Ca^{2+}_{total})	**Ionized calcium** (Ca^{2+}_{ion})
Normal	8.5–10.3 mg/dL	4.5–5.6 mg/dL
Mild	Less than 12 mg/dL	Less than 8 mg/dL
Moderate	12–13.9 mg/dL	8–9.9 mg/dL
Severe	14 mg/dL or higher	10 mg/dL or higher

Note. From "Calcium, Magnesium, and Phosphate Abnormalities in the Emergency Department," by W. T. W. Chang, B. Radin, and M. T. McCurdy, 2014, *Emergency Medicine Clinics of North America*, Vol. 32, Issue 2, pp. 349–366. doi: 10.1016/j.emc.2013.12.006; "Hypercalcemia Associated With Cancer," A. F. Stewart, 2005, *New England Journal of Medicine*, Vol. 352, Issue 4, pp. 373–379.

environment, more of the binding sites on albumin are occupied by hydrogen ions in an effort to compensate for the increased free hydrogen ion concentration in the serum. This leaves less space for calcium to bind, leading to an increase in ionized calcium that is not always reflected in the total serum calcium concentration (Blaine, Chonchol, & Levi, 2014).

If total serum calcium concentration is the only value available, it is important to also obtain an albumin level and blood pH in an effort to account for these variables. A corrected Ca^{2+}_{total} concentration that accounts for a low albumin level can be calculated through the following method:

$$\text{Corrected Total } Ca^{2+} \frac{\text{mg}}{\text{dL}} = \text{Total Measured Calcium} \left(\frac{\text{mg}}{\text{dL}}\right) + 0.8 \left(4 | \text{measured albumin} \left[\frac{\text{g}}{\text{dL}}\right]\right)$$

One pitfall of this approach is the possibility of an imprecise estimation. For example, in the presence of rare myelomas where calcium-binding immunoglobulins are produced, it could lead to an overestimation of ionized calcium. Although this calculation of Ca^{2+}_{ion} is a reasonable option, a directed measurement of serum ionized calcium is preferred (Stewart, 2005).

EPIDEMIOLOGY

Malignancy is the number 1 cause of hypercalcemia in the ED, with hyperparathyroidism being the second most common. Few articles have been published that discuss the epidemiology of malignancy-associated hypercalcemia (MAH) in the ED, but those that have been published found that one third to one half of the patients who present with hypercalcemia have an underlying malignancy (Lee et al., 2006). The most recent study in 2013 looked at all patients who presented to the ED over 3 years, which included 14,984 that had a serum calcium level measured (Lindner et al., 2013). Of these patients, 116 (0.77%) were found to have hypercalcemia, defined as a level greater than 10.2 mg/dL (Lindner et al., 2013). This study complemented other studies and found that the most common cause of hypercalcemia was malignancy, followed by hyperparathyroidism. However, an interesting trend that appeared in this study that has been observed over the past few decades is the increase in secondary compared to primary hyperparathyroidism. This has been attributed to the increasing number of patients with chronic renal insufficiency and is expected to continue to increase with time (Greaves, Grant, Heath, Michael, & Adu, 1992).

About one-fourth of all patients with a malignancy will develop hypercalcemia, with Ca^{2+}_{total} often exceeding 13 mg/dL, well outside of the normal range of 8.5–10.3 mg/dL (Lindner et al., 2013). Patients with MAH are more likely to be symptomatic and have a

lower survival rate than those with hypercalcemia attributable to another cause, such as hyperparathyroidism or a granulomatous disease. This is most likely due to higher serum calcium levels in patients with an underlying malignancy, as well as the advanced stage of disease upon presentation.

PATHOPHYSIOLOGY

As mentioned earlier, ionized calcium that is freely filtered at the glomerulus in the kidney plays a vital role in biologic processes that are integral to survival, such as nerve impulse transmission, muscular contraction, and hormone secretion. A healthy adult consumes about 1 g of calcium per day, with dietary intake being the only way that stores of calcium can be restored. Eight hundred milligrams of calcium consumed is excreted in feces, and 200 mg is absorbed by the small intestine into the bloodstream, leading to 200 mg of calcium eliminated in the urine daily (Blaine et al., 2014).

Calcium is regulated via three main mechanisms including intestinal absorption, renal reabsorption, and exchange from bone (see Figure 1). Each of these mechanisms is under control of PTH (parathyroid hormone) and vitamin D. Parathyroid glands increase PTH secretion in response to low calcium and elevated phosphorous, and PTH gene transcription is increased by glucocorticoids and estrogen. One way in which PTH increases serum calcium concentration is by binding to specific receptors on osteoblasts, or bone-forming cells, leading to an increase in receptor activator of nuclear factor-κB ligand (RANK-L). RANK-L then binds to its receptor (RANK) and stimulates osteoclasts, resulting in subsequent bone resorption (Crowley & Gittoes, 2013).

Parathyroid hormone has two important effects on the kidneys. First, it upregulates renal 1-α-hydroxylase, which converts inactive

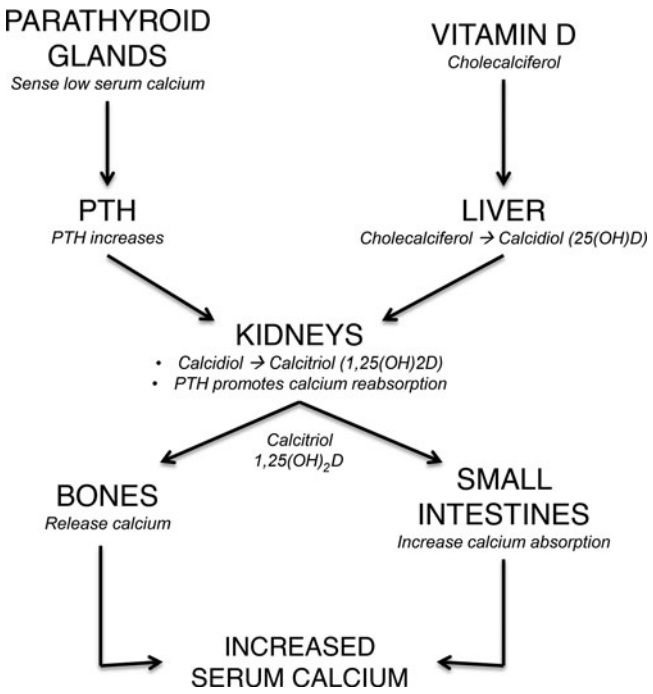

Figure 1. Effects of parathyroid hormone (PTH) and vitamin D. From "How to Approach Hypercalcemia," by R. Crowley and N. Gittoes, 2013, *Clinical Medicine*, Vol. 13, Issue 3, pp. 287–290.

vitamin D (25(OH)D) into active vitamin D ($1,25(OH)_2D$). This directly causes increased intestinal absorption of calcium and decreased renal calcium excretion and may play a synergistic role with PTH on bone resorption (Dusso, Brown, & Slatopolsky, 2005). Roughly 10 g of calcium is filtered daily, and 98%–99% of this filtered calcium must be reabsorbed by the renal tubules to maintain calcium homeostasis. Parathyroid hormone increases active calcium reabsorption at the proximal tubule of the kidney, accounting for 10%–15% of the renal calcium reabsorption that occurs. The majority of the remaining calcium that must be absorbed occurs passively in the proximal tubule, similar to sodium and water, and the loop of Henle, with the terminal nephron being the major site for regulation of calcium excretion (Blaine et al., 2014).

A significant rise in serum calcium associated with malignancy can be attributed to one of four causes. The majority of patients experience hypercalcemia secondary to secretion of PTH-related protein (PTHrP) from malignant tumors, which mimics the aforementioned actions of PTH (Stewart, 2005). Hypercalcemia caused by PTHrP, also referred to as humoral hypercalcemia of malignancy, is the most common cause of MAH, which accounts for roughly 80% of all MAH cases. Humoral hypercalcemia of malignancy is most commonly associated with squamous cell cancer (e.g., lung), renal cancer, ovarian cancer, endometrial cancer, lymphoma, and breast cancer.

Another common cause of elevated serum calcium is bone resorption due to the presence of malignant cells within the bone marrow. The release of local inflammatory factors from the metastases indirectly stimulates osteoclast production, resulting in diffuse bone loss or localized lesions. This osteolytic hypercalcemia caused by bone metastases can be found in lung and breast cancer, multiple myeloma, lymphoma, and leukemia, and accounts for about 20% of MAH cases (Wagner & Arora, 2014).

The final and two rarest causes of MAH are ectopic hyperparathyroidism and vitamin D secreting lymphomas. An increase in $1,25(OH)_2D$ in some lymphomas (most commonly Hodgkin's) accounts for less than 1% of MAH cases and leads to an increase in serum calcium via the aforementioned mechanisms (Seymour & Gagel, 1993). Ectopic hyperparathyroidism results in secretion of authentic PTH (as opposed to secretion of PTHrP) from the chief cells of the parathyroid gland and has been seen in eight well-documented patients to date.

CLINICAL PRESENTATION

The presence or absence of symptoms in patients with MAH is dependent on both the degree of hypercalcemia and the rate in which serum calcium concentrations are rising. According to a publication on acute hypercalcemia management by the Society for Endocrinology's Clinical Committee (2013), patients presenting with mild hypercalcemia often lack symptoms and do not require urgent correction. However, patients with moderate hypercalcemia may be asymptomatic or symptomatic. Prompt treatment is indicated in symptomatic patients or patients with total serum calcium levels exceeding 14 mg/dL due to the risk of dysrhythmias and coma.

Cardiovascular manifestations of hypercalcemia are the most concerning adverse effects. In addition to the symptoms listed in Table 2, many patients with hypercalcemia related to malignancy also develop hypokalemia, which further contributes to the risk of arrhythmias in this population. Although calcium exhibits positive inotropic effects at levels less than 15 mg/dL, severe hypercalcemia may cause myocardial depression and can be grave enough to lead to atrioventricular block, with levels greater than 20 mg/dL leading to cardiac arrest (Chang, Radin, & McCurdy, 2014).

Other common clinical features of hypercalcemia include gastrointestinal, central nervous system, renal, and dermatologic manifestations (see Table 2). Nephrogenic diabetes insipidus is a common renal complication of hypercalcemia caused by calcium

Table 2. Symptoms of hypercalcemia

Cardiovascular	Gastrointestinal	Renal	Neurologic	Miscellaneous
Shortened ST segments and QT intervals	Nausea	Nephrogenic diabetes insipidus	Fatigue	Pruritus
Depressed ST segments	Vomiting	Acute kidney injury	Depression	Peptic ulcer disease
Widened T waves	Anorexia		Weakness	Abdominal pain
Prolonged PR and QRS intervals	Constipation		Hyporeflexia	Bone pain
			Confusion	Pancreatitis

Note. From "Oncologic Metabolic Emergencies," by J. Wagner and S. Arora, 2014, *Emergency Medicine Clinics of North America*, Vol. 32, pp. 509–525. doi: 10.1016/j.emc.2014.04.003.

deposition over time. Nephrogenic diabetes insipidus results in increased urine output, which further exacerbates the volume depletion caused by decreased oral intake, nausea, and vomiting. In addition, activation of the calcium sensing receptor leads to sodium excretion via inhibition of the $Na^+/K^+/Cl^-$ channel in the thick ascending loop of Henle, leading to increased excretion of water (Reagan, Pani, & Rosner, 2014). Acute kidney injury may occur as a result of this significant volume loss, or calcium deposition in the kidney. Neurologic symptoms are more pronounced during moderate hypercalcemia in elderly patients, those with cognitive deficits at baseline, or those being treated with strong narcotics or sedatives (Wagner & Arora, 2014). Other patients usually remain alert until their serum calcium levels rise greater than 14 mg/dL (Stewart, 2005). Neurologic complications may progress to hallucinations, seizures, and coma in severe hypercalcemia if left untreated (Chang et al., 2014).

DIAGNOSTIC CRITERIA

Once the presence of hypercalcemia is confirmed, it is essential to determine the cause (see Figure 2). Malignancy-associated hypercalcemia and primary hyperparathyroidism account for about 80%–90% of cases of elevated calcium (Wagner & Arora, 2014). To determine whether either condition is the cause, the level of intact PTH must be measured. This level is expected to be low in the presence of hypercalcemia secondary to the negative feedback inhibition of elevated serum calcium on PTH. Therefore, an elevated PTH level is most commonly indicative of primary hyperparathyroidism. In addition, chronic hypercalcemia with a total serum calcium level less than 12 mg/dL is usually indicative of primary hyperparathyroidism, whereas acutely severe hypercalcemia is more common with MAH. If intact PTH levels are low, a diagnosis of humoral hypercalcemia of malignancy can be aided by the presence of PTHrP in the blood. However, it normally takes about a week to obtain PTHrP levels as it is a send-out laboratory test at most hospitals and therefore is not likely relevant in the ED setting.

A measurement of $1,25(OH)_2D$ is also suggested when intact PTH levels are low and disease states such as $1,25(OH)_2D$-secreting lymphomas are being considered in the differential diagnosis. While there are some exceptions, symptomatic MAH does not typically occur until later stages of the disease so the tumors present are generally large enough to be seen on a CT scan. Because of the stage of disease, the average survival of patients diagnosed with MAH is only weeks postdiagnosis, with 50% of patients dying within a month of diagnosis (McCurdy & Shanholtz, 2012).

MANAGEMENT OPTIONS

Treatment of MAH is centered upon restoring normal fluid volume and decreasing the

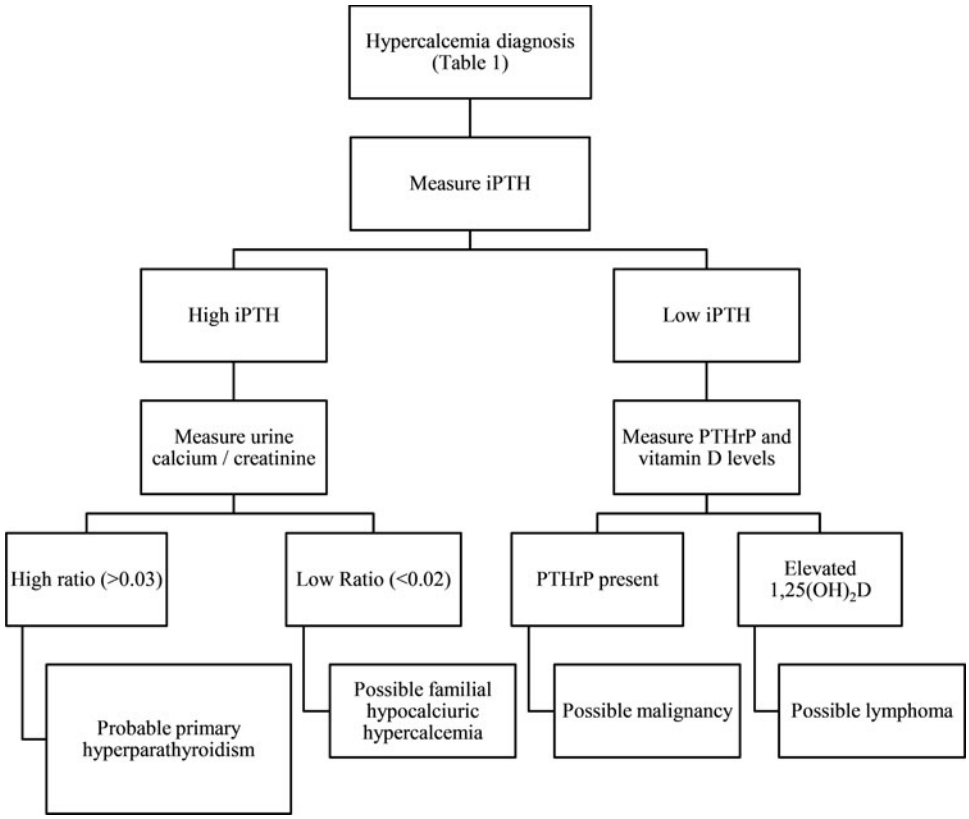

Figure 2. Diagnosis of hypercalcemia. iPTH = intact PTH; normal iPTH = 11–54 pg/mL; normal $1,25(OH)_2D$ = 24–65 pg/mL; ectopic hyperparathyroidism is rare and can only be distinguished from primary hyperparathyroidism by the presence of an adenoma. PTH = parathyroid hormone. From "Oncologic Metabolic Emergencies," by J. Wagner and S. Arora, 2014, *Emergency Medicine Clinics of North America*, Vol. 32, pp. 509–525. doi:10.1016/j.emc.2014.04.003.

release of calcium from bone. Since most patients present to the ED in a state of volume depletion, administering intravenous fluids in symptomatic or severely hypercalcemic individuals (based on measured Ca^{2+}_{ion}) is the first critical step in management of MAH (see Figure 3). Most clinicians will choose to first administer a normal saline bolus of 1–2 L, followed by a saline infusion with an initial rate of 200–250 mL/hr and then titrate fluids to produce a urine output of 100–150 mL/hr.

Although restoration of fluid volume will aid in diluting the serum calcium concentration, the main purpose of fluid replenishment is to increase calcium excretion. An increased intravascular volume will lead to an increase in the glomerular filtration rate, which increases filtration of calcium and decreases reabsorption of calcium at the proximal tubule. In addition, as the amount of sodium and water introduced to the distal tubule increases, there is a rise in calciuresis (Bilezikian, 1992).

Another important consideration is the increasing use of balanced solutions in critically ill patients and institutions. Although some balanced solutions are calcium-free (i.e., Plasma-Lyte and Normosol-R), there are others that contain calcium such as Lactated Ringer's, which has a calcium concentration of 2 mmol/L (8 mg/dL) (Young & Joannidis, 2014). As long as the calcium concentration of the solution is less than the patient's serum calcium concentration, the solution can still be expected to lower calcium levels over

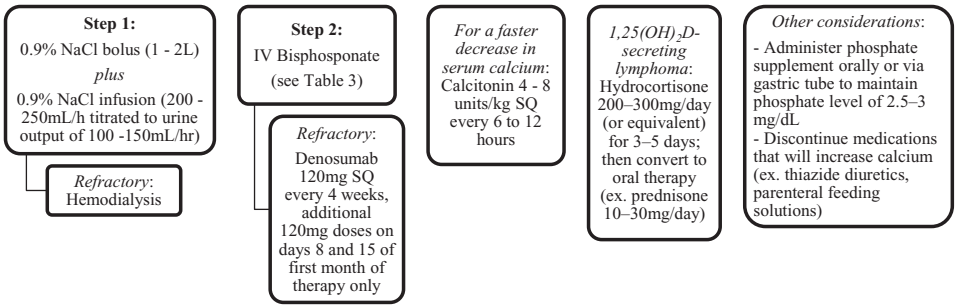

Figure 3. Treatment of malignancy-associated hypercalcemia. From "Approach to Diagnosis and Treatment of Hypercalcemia in a Patient With Malignancy," by P. Reagan, A. Pani, and M. H. Rosner, 2014, *American Journal of Kidney Diseases,* Vol. 63, Issue 1, pp. 141–147. doi: 10.1053/j.ajkd.2013.06.025. From "Hypercalcemia Associated With Cancer," by A. F. Stewart, 2005, *New England Journal of Medicine,* Vol. 352, Issue 4, pp. 373–379.

time. There is currently no evidence comparing intravascular volume replacement with normal saline versus another agent. However, the increased experience with saline and its calciuretic effect would support its use as a first-line agent. Normal saline is therefore still more commonly recommended than a balanced solution. Fluid replacement may be used in patients with severe kidney failure or congestive heart failure, but these patients should be closely monitored for fluid overload or worsening symptoms. Unfortunately, fluid administration is often insufficient and will achieve normal serum calcium levels in less than 30% of patients (McCurdy & Shanholtz, 2012). If fluid replacement is not effective, or if fluid repletion will not lower calcium quickly enough in other patients (e.g., calcium concentration greater than 18 mg/dL and significant neurologic findings), hemodialysis is then indicated (Stewart, 2005). However, hemodialysis is not always a feasible option immediately. Several obstacles often stand in the way of a patient receiving urgent hemodialysis that must be kept in mind when deciding upon a course of action, such as availability of hemodialysis equipment and the patient lacking vascular access for hemodialysis.

After fluid administration, the first-line treatment option for MAH is intravenous administration of bisphosphonates. Bisphosphonates have a high affinity for the mineral component of bone (hydroxyapatite), which allows them to reach very high skeletal concentrations. Based on this affinity for bone, bisphosphonates are able to exert effects on disorders with enhanced bone turnover, such as MAH, when bone resorption prevails. By binding to bone, bisphosphonates directly inhibit osteoclasts' ability to bind and initiate resorption. In addition, bisphosphonates may induce osteoclast apoptosis by inhibiting farnesyl pyrophosphate synthase, an enzyme that controls intracellular levels of several essential proteins for multiple biologic processes (Drake, Clarke, & Lewiecki, 2015). Bisphosphonate therapy initiation is not always indicated in the ED, although most experts recommend beginning therapy in the ED because of the delayed time of effect. Oral absorption of these medications is very low (bioavailability of 1%–2%), and therefore only intravenous administration is recommended in this setting. There are three bisphosphonates currently available in intravenous form, but only pamidronate and zoledronate (dosing provided in Table 3) are approved by the Food and Drug Administration for the treatment of MAH.

Bisphosphonates are able to produce a reduction in serum calcium in 24–48 hours, with complete normalization of the corrected serum calcium occurring in 4–10 days

Table 3. Bisphosphonate dosing recommendations

Drug Name	Zoledronate	Pamidronate
Dose	4 mg	90 mg
Diluent	50 mL 0.9% NaCl or D5W	50–200 mL 0.9% NaCl or D5W
Administration time	15 min	2 hr
Patients with complete response by:		
Day 4	45.3%	33.3%
Day 7	82.6%	63.6%
Duration of complete response (days)	32	18
Time to relapse (days)	30	17

Note. From "Zoledronic Acid Is Superior to Pamidronate in the Treatment of Hypercalcemia of Malignancy: A Pooled Analysis of Two Randomized, Controlled Clinical Trials," by P. Major, A. Lortholary, J. Hon, E. Abdi, G. Mills, H. D. Menssen, . . . J. Seaman, 2001, *Journal of Clinical Oncology*, Vol. 19, Issue 2, pp. 558–567.

(Major et al., 2001). The decreased serum calcium level is normally maintained for about 2–3 weeks and may be sustained for up to 4 weeks. The use of bisphosphonates is currently controversial, especially in a patient population that is at an increased risk of kidney injury. Zoledronate has been shown to cause tubular damage and is contraindicated in patients with a creatinine clearance less than 35 mL/min and patients with acute renal impairment. There is less evidence regarding tubular damage with the use of pamidronate and therefore may be an option in this patient population if it is used with caution (Davenport, Goel, & Mackenzie, 1993). Some clinicians, for example, may choose to administer pamidronate at a reduced dose or rate in this patient population in an attempt to prevent renal complications (Berenson et al., 1997).

Zoledronate has some advantages over pamidronate, including faster onset, higher response rate, and longer duration of action (see Table 3). A pooled analysis of two randomized, controlled clinical trials portrays evidence in favor of zoledronate as the first-line option for MAH (Major et al., 2001). These double-blind, double-dummy, multicenter trials compared the rate of complete response (defined by a corrected calcium concentration less than 10.8 mg/dL), response duration, and time to relapse between zoledronate (4 and 8 mg) and pamidronate. Both doses of zoledronate showed significantly improved primary outcomes compared with pamidronate, although the difference in average nadir serum calcium levels was small (zoledronate vs. pamidronate: 9.8 mg/dL vs. 10.5 mg/dL). By the 10th day after the study drugs were administered, 88.4% of patients receiving zoledronate (4 mg) achieved complete remission, compared with 69.7% of patients receiving pamidronate. Although these differences were statistically significant, it is unknown whether these small differences have an effect on clinically significant outcomes such as mortality. In addition, pamidronate is significantly less costly (average wholesale price $104 vs. $713 for a dose of zoledronate) and is associated with less renal failure (Novartis Pharmaceuticals, 2002; 2008). Both pamidronate and zoledronate are acceptable choices and the decision depends on the discretion of the provider and institution, the convenience, price of administration, and patient-specific considerations.

If the patient is diagnosed with a $1,25(OH)_2D$-secreting lymphoma or a malignancy that causes excess 1-α-hydroxylase, glucocorticoids may be beneficial (see Figure 3). Glucocorticoids work particularly well in these patients by decreasing extrarenal $1,25(OH)_2D$ production, inhibiting osteoclastic bone resorption through a decreased

tumor production of inflammatory mediators, and exerting direct tumorlytic effects (Clines & Guise, 2005). However, clinicians should be aware that effects may not be apparent for more than 4 days and steroids should be used with caution because they may precipitate tumor lysis syndrome (Society for Endocrinology's Clinical Committee, 2013). If a response is not seen by the 10th day of therapy, glucocorticoids should be discontinued (Clines & Guise, 2005).

Other therapeutic agents used to lower serum calcium include loop diuretics and calcitonin. Loop diuretics inhibit the reabsorption of calcium and sodium in the ascending loop of Henle and at the distal tubule and promote calcium secretion, further decreasing serum calcium levels. However, they will also result in additional volume loss and electrolyte abnormalities and are therefore only recommended in volume overloaded patients (LeGrand, Leskuski, & Zama, 2008). If electrolyte disturbances do occur, clinicians must be wary of replacing electrolytes too aggressively. For example, if a patient comes in with hypokalemia and acute kidney injury in addition to hypercalcemia, it is important to be cautious so the patient does not become hyperkalemic secondary to excessive potassium administration in the presence of renal insufficiency. In addition, replacing potassium may become troublesome if a patient has limited intravenous access, and it is therefore important to know the fast-acting oral supplements available at your institution.

Calcitonin directly inhibits bone resorption and quickly promotes renal excretion of calcium, leading to a decrease in serum calcium 2 hr after administration. Calcitonin may be given intramuscularly, although subcutaneous administration is preferred (see Figure 3). Calcitonin carries a risk of immediate hypocalcemia, rebound hypercalcemia, and the propensity to develop tachyphylaxis after 2–3 days of therapy. Providers often administer calcitonin when a rapid decrease in calcium is needed in patients who are experiencing severe side effects (e.g., cardiovascular, neurologic) as a temporizing measure before the onset of the calcium-lowering effects of intravenous bisphosphonates (Stewart, 2005).

Denosumab is a monoclonal antibody that binds to RANK-L, leading to inhibition of osteoclast differentiation and bone resorption. A recent case report described the effective use of denosumab (a single subcutaneous 60-mg dose) in a 50-year-old woman with MAH who was unable to receive bisphosphonates because of renal failure (Bech & de Boer, 2012). Bech and de Boer (2012) suggest a possible niche for denosumab therapy in patients with MAH and renal failure, but more studies must be completed to support this therapy. On the basis of an open-label, single-arm study that included patients diagnosed with MAH unresponsive to bisphosphonate therapy, denosumab was approved by the Food and Drug Administration for treatment of MAH refractory to bisphosphonates in late 2014 (see Figure 3) (Hu et al., 2014). However, monoclonal antibodies are extremely costly and logistics often make them a less than ideal treatment option for emergency management of MAH, excluding any viable use in the ED.

Although these therapies may treat elevated calcium levels, they will not treat the underlying cause. It is important to understand that the current therapy of MAH is a means of keeping the patient stable enough to begin cancer treatment or palliative care, and calcium-lowering therapy alone does not reduce mortality rate (McCurdy & Shanholtz, 2012). Therefore, it is important that these patients immediately receive an oncology consult to create a proper treatment plan.

MONITORING OF INTERVENTIONS

Once therapy is initiated and the patient is stabilized, total serum calcium and ionized calcium concentrations should be measured 7–10 days after intravenous administration of bisphosphonates when they are expected to normalize. Although bisphosphonates should begin to exert a small effect in the first

2 days of therapy, it is unnecessary to monitor calcium levels this early if the patient is being treated on an outpatient basis. Therefore, there is minimal monitoring that must be emergently performed. Patients with MAH will often have altered serum concentrations of potassium, magnesium, and phosphorous, and by administering large amounts of fluid, there is a risk of worsening these abnormalities. If furosemide is used in the case of volume overload, this could be even more problematic. Electrolyte levels must be monitored closely to avoid further complications, with the frequency of monitoring dependent on patient acuity and choice of therapy. For example, a patient experiencing cardiovascular side effects will most likely be placed on telemetry and monitored more frequently than a patient presenting with gastrointestinal discomfort. Similarly, the administration of calcitonin for rapid correction of hypercalcemia would warrant more frequent monitoring of calcium levels. Volume status should be assessed on the basis of the patient's fluid intake, urinary output, and weight.

PATIENT DISPOSITION

Some patients may require immediate admission to the hospital based on their symptoms, acuity, risk of decompensation, and need for fluid replacement. Other patients may be stable enough to seek treatment for their malignancy to avoid recurrent MAH in an outpatient setting. Patients who are stabilized usually require oncology care and are sent home to follow-up for treatment of the underlying malignancy. If treatment initiation of the underlying malignancy does not yield a normalized serum calcium level after a few weeks (i.e., after the bisphosphonate therapy is no longer effective), the patient may need to return for repeated intravenous administration of an bisphosphonate as needed until they are no longer hypercalcemic.

CONCLUSION

Malignancy-associated hypercalcemia is a severe and acute form of hypercalcemia, which often requires the initiation of treatment in the ED. Because of the wide variety of manifestations and differing rates at which serum calcium rises in each patient, treatment is not always required. Patients who are symptomatic or have a serum calcium level greater than 14 mg/dL will always be treated because of the risk of cardiac effects and coma. Management consists of adequate hydration, intravenous bisphosphonate therapy with zoledronate or pamidronate, and correction of other abnormal electrolyte levels. Although there is evidence to support the use of zoledronate over pamidronate, it is still unclear if these differences are clinically significant. The choice of product is therefore up to the institution and providers based on patient-specific information, cost, and convenience of administration. There is no treatment for MAH, which has a demonstrated effect on mortality, and therefore it is associated with a very poor prognosis. Current treatment options for MAH are viewed as a means of stabilizing the patient until the underlying malignancy can be treated.

REFERENCES

Bech, A., & de Boer, H. (2012). Denosumab for tumor-induced hypercalcemia complicated by renal failure. *Annals of Internal Medicine*, *156*(12), 906–907. doi:10.7326/0003-4819 156-12-201206190-00026.

Berenson, J. R., Rosen, L., Vescio, R., Lau, H. S., Woo, M., Sioufi, A., . . . Seaman, J. J. (1997). Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *The Journal of Clinical Pharmacology*, *37*(4), 285–290.

Bilezikian, J. P. (1992). Management of acute hypercalcemia. *New England Journal of Medicine*, *326*(18), 1196–1203.

Blaine, J., Chonchol, M., & Levi, M. (2014). Renal control of calcium, phosphate, and magnesium homeostasis. *Clinical Journal of the American Society of Nephrology*, doi:10.2215/CJN.09750913.

Chang, W. T. W., Radin, B., & McCurdy, M. T. (2014). Calcium, magnesium, and phosphate abnormalities in the emergency department. *Emergency Medicine Clinics of North America*, *32*(2), 349–366. doi:10.1016/j.emc.2013.12.006.

Clines, G. A., & Guise, T. A. (2005). Hypercalcaemia of malignancy and basic research on mechanisms responsible for osteolytic and osteoblastic metastasis

to bone. *Endocrine-Related Cancer*, *12*(3), 549–583. doi:10.1677/erc.1.00543.

Crowley, R., & Gittoes, N. (2013). How to approach hypercalcemia. *Clinical Medicine*, *13*(3), 287–290.

Davenport, A., Goel, S., & Mackenzie, J. C. (1993). Treatment of hypercalcaemia with pamidronate in patients with end stage renal failure. *Scandinavian Journal of Urology and Nephrology*, *27*(4), 447–451.

Drake, M. T., Clarke, B. L., & Lewiecki, E. M. (2015). The pathophysiology and treatment of osteoporosis. *Clinical Therapeutics*, *37*(8), 1837–1850.

Dusso, A. S., Brown, A. J., & Slatopolsky, E. (2005). Vitamin D. *American Journal Physiology Renal Physiology*, *289*(1), F8–F28. doi:10.1152/ajprenal.00336.2004.

Greaves, I., Grant, A. J., Heath, D. A., Michael, J., & Adu, D. (1992). Hypercalcaemia: changing causes over the past 10 years. *British Medical Journal*, *304*(6837), 1284.

Hu, M. I., Glezerman, I. G., Leboulleux, S., Insogna, K., Gucalp, R., Misiorowski, W., . . . Jain, R. K. (2014). Denosumab for treatment of hypercalcemia of malignancy. *Journal of Clinical Endocrinology & Metabolism*, *99*(9), 3144–3152. doi:10.1210/jc.2014-1001.

Lee, C. T., Yang, C. C., Lam, K. K., Kung, C. T., Tsai, C. J., & Chen, H. C. (2006). Hypercalcemia in the emergency department. *American Journal of the Medical Sciences*, *331*(3), 119–123.

LeGrand, S. B., Leskuski, D., & Zama, I. (2008). Narrative review: Furosemide for hypercalcemia: An unproven yet common practice. *Annals of Internal Medicine*, *149*(4), 259–263.

Lindner, G., Felber, R., Schwarz, C., Marti, G., Leichtle, A. B., Fiedler, G. M., . . . Exadaktylos, A. K. (2013). Hypercalcemia in the ED: Prevalence, etiology, and outcome. *American Journal of Emergency Medicine*, *31*(4), 657–660. doi:10.1016/j.ajem.2012.11.010.

Major, P., Lortholary, A., Hon, J., Abdi, E., Mills, G., Menssen, H. D., . . . Seaman, J. (2001). Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. *Journal of Clinical Oncology*, *19*(2), 558–567.

McCurdy, M. T., & Shanholtz, C. B. (2012). Oncologic emergencies. *Critical Care Medicine*, *40*(7), 2212–2222. doi:10.1097/CCM.0b013e31824e1865.

Novartis Pharmaceuticals. (2002). *Aredia* [Package insert]. East Hanover, NJ: Author.

Novartis Pharmaceuticals. (2008). *Zometa* [Package insert]. East Hanover, NJ: Author.

Reagan, P., Pani, A., & Rosner, M. H. (2014). Approach to diagnosis and treatment of hypercalcemia in a patient with malignancy. *American Journal of Kidney Diseases*, *63*(1), 141–147. 10.1053/j.ajkd.2013.06.025.

Seymour, J. F., & Gagel, R. F. (1993). Calcitriol: The major humoral mediator of hypercalcemia in Hodgkin's disease and non-Hodgkin's lymphomas. *Blood*, *82*(5), 1383–1394.

Society for Endocrinology. (2013). *Emergency endocrine guidance: Acute hypercalcaemia*. Retrieved from https://www.endocrinology.org/policy/docs/13-02_EmergencyGuidance-AcuteHypercalcaemia.pdf

Stewart, A. F. (2005). Hypercalcemia associated with cancer. *New England Journal of Medicine*, *352*(4), 373–379.

Wagner, J., & Arora, S. (2014). Oncologic metabolic emergencies. *Emergency Medicine Clinics of North America*, *32*, 509–525. doi:10.1016/j.emc.2014.04.003

Young, P. J., & Joannidis, M. (2014). Crystalloid fluid therapy: Is the balance tipping towards balanced solutions? *Intensive Care Medicine*, *40*(2), 1966–1968. doi:10.1007/s00134-014-3531-1

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