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CE **Article #5 (1.5 contact hours)**
Refereed Peer Review

Humoral Hypercalcemia of Malignancy: Diagnosis and Treatment*

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KEY FACTS

- Differentiating humoral hypercalcemia of malignancy with secondary renal dysfunction from renal disease with secondary hypercalcemia can be difficult.
- All necessary diagnostic samples should be collected before initiating therapy that may affect the ability to determine the underlying cause.
- Supportive therapy should be provided until an etiologic diagnosis can be made and specific treatment begun.

ABSTRACT: The diagnosis of humoral hypercalcemia of malignancy begins with a thorough history and physical examination. After confirming the presence of true hypercalcemia, the diagnostic plan should be developed to include testing such as radiography of the thorax and abdomen; ultrasonography of the abdomen; aspiration cytology of lymph nodes and bone marrow; and, potentially, specialized blood tests to determine parathyroid hormone, parathyroid hormone–related protein, ionized calcium, and calcidiol levels. Supportive therapy with diuresis and additional drug therapy (e.g., diuretics and glucocorticoids as needed) helps protect the body from the detrimental effects of hypercalcemia until an etiologic diagnosis is made and more specific therapy initiated. In refractory cases, other therapies, including salmon calcitonin, bisphosphonates, and sodium bicarbonate, may be indicated. Most patients have a good quality of life while the underlying cancer is in remission.

The diagnosis of humoral hypercalcemia of malignancy (HHM) can often be established simply by conducting a biochemistry panel and rectal palpation in the dog or a fine-needle aspiration of a peripheral lymph node. In more challenging cases, however, the diagnosis of HHM may require specialized blood tests, diagnostic imaging, biopsies, and assessment of response to therapy. Therapy begins with IV fluids and diuretics, with more aggressive drug treatments as required, and progresses to specific treatment for the underlying neoplastic disease.

MEASURING BLOOD CALCIUM

The first diagnostic step when hypercalcemia is detected on a routine serum biochemistry panel should be to confirm that it is real. The possibility of spurious test results should be ruled out whenever an elevated total serum calcium (Ca) value appears on a biochemistry panel. Ideally, a fasting sample should be submitted because sample conditions (lipemia or hemolysis) can artifactually increase the total serum Ca values reported by colorimetric analyzers. In the presence of lipemia or hemolysis, it is recommended that the clinical pathology laboratory or

*A companion article on pathophysiology and clinical signs appears on p. 122.

owner's manual (for in-house analyzers) be used to determine the effect of serum sample quality on total serum Ca values. After confirming the presence of elevated Ca on a fasted sample, an ionized Ca value should be determined because it is a better reflection of the biologically active form of Ca, the form of Ca that interacts with cellular receptors and enzymes.[1]

Ionized Ca level determination is the best method for monitoring Ca homeostasis but, unfortunately, is often the least readily available tool. Samples used for ionized Ca determination should be handled anaerobically (similarly to a blood gas sample) and according to reference laboratory guidelines because pH, temperature, and carbon dioxide content can alter reported ionized Ca values.[1,2] Ionized Ca determinations are typically conducted only at reference laboratories but may also be conducted in the practice setting by using in-house analyzers. Unfortunately, in-house analyzers were shown in one study to underestimate ionized Ca values.[3] In healthy dogs, ionized Ca values can be estimated from the total serum values: Ionized Ca is approximately 55% of the total serum Ca.[1,2] In adult dogs (older than 12 months of age), accuracy can be further improved by first correcting the total serum Ca for the serum albumin concentrations as follows[1,2,4,5]:

$$\text{Adjusted total Ca}^{a}\ (\text{mg/dl}) = \text{total Ca (mg/dl)} - \text{albumin (g/dl)} + 3.5$$

Unfortunately, the concentration of ionized Ca cannot be accurately estimated in cats or sick dogs based on a percentage of total serum Ca because it is affected by many factors, including pH, serum protein concentrations and affinity, and complexed Ca concentrations.

The usefulness of estimating the ionized Ca value is further limited by the severity of the disease process. For example, in canine lymphoma, a very high ionized Ca concentration correlates well with a high total serum Ca value. This is in contrast to milder increases in the ionized Ca level, which has a poorer correlation to the total serum Ca value.[1] This may be explained by the relative magnitude of changes in the ionized versus total serum Ca level. Therefore, milder cases of HHM may be overlooked if the ionized Ca value is not evaluated. The reported prevalence of HHM may potentially be underestimated if the ionized Ca level is not evaluated in all cases of lymphosarcoma. In cats, only moderate correlation is recognized between ionized and total serum concentrations in both sick and healthy patients.

[a]Adjusted Ca is not applicable for cats and immature dogs (younger than 1 year of age) and should not be used to correct a normal total serum Ca level outside of the normal range.

Differential Diagnosis of Hypercalcemia

The most commonly reported cause of pathologic hypercalcemia in dogs and cats is HHM, with a frequency of approximately 30% to 60% in hypercalcemic dogs[6] and approximately 30% in hypercalcemic cats.[25] Other potential causes of hypercalcemia include laboratory error, hyperalbuminemia, acute or chronic renal failure, primary hyperparathyroidism, granulomatous diseases (including blastomycosis in dogs and nocardiosis in cats),[7,10,13,20] toxins (vitamin D metabolites),[a,b,17,21] and hypoadrenocorticism.[c,1,2,25]

A thorough medical history, physical examination, and subsequent workup lead to the cause of the disease process in most cases, although 2.5% of cases of hypercalcemia remain undiagnosed in dogs[6] and 12.5% remain idiopathic in cats.[25]

HARD IONS (a mnemonic originating from The Ohio State University) is helpful in recalling the differential diagnosis of hypercalcemia:

- **H** Hyperparathyroidism/HHM
- **A** Addison's disease (hypoadrenocorticism)
- **R** Renal disease
- **D** Vitamin D (toxicosis or granulomatous disease)/Dehydration
- **I** Idiopathic (particularly in cats)
- **O** Osteolytic
- **N** Neoplastic: HHM and local osteolytic hypercalcemia
- **S** Spurious

[a]Fan TM, Simpson KW, Trasti S, et al: Calcipotriol toxicity in a dog. *J Small Anim Pract* 39:581–586, 1998.
[b]Weller RE, Hoffman WE: Renal function in dogs with lymphosarcoma and associated hypercalcemia. *J Small Anim Pract* 33:61–66, 1992.
[c]Kleiter M, Hirt R, Kirtz G, Day MJ: Hypercalcemia associated with chronic lymphocytic leukemia in a giant schnauzer. *Aust Vet J* 79:335–338, 2001.

DIAGNOSIS

The initial diagnostic approach to a patient with suspected HHM begins with a thorough review of signalment and history and a complete physical examination. Because the most commonly reported cause of HHM is lymphosarcoma, evaluation of peripheral lymph nodes with aspiration cytology (even if they are normal on palpation) is warranted in patients with unexplained hypercalcemia.[1,2,4,6–9] Thorough palpation of the abdomen may reveal splenomegaly, lymphadenopathy, and/or hepatomegaly. A thorough rectal examination, with careful palpation of the anal sac area, should be performed in dogs to look for perianal masses and to evaluate the sublumbar lymph nodes.

Abdominal (two views) and thoracic (three views) radiographs should be evaluated for metastasis, organomegaly, and lymphadenopathy. A thorough evaluation of the mediastinal space is essential because this is a particularly common location for lymphosarcoma in hypercalcemic patients. The pelvis and vertebrae should be evaluated on these radiographs for evidence of local osteolytic or proliferation lesions that may be suggestive of neoplasia, such as metastatic disease or multiple myeloma,[10] or infectious processes, such as blastomycosis. Abdominal ultrasonography should then be performed to substantiate the findings of abdominal radiography and to aid in collecting aspiration cytology or needle biopsy samples. Bone marrow aspiration and core biopsy may be performed to investigate for the presence of malignant lymphocytes or plasma cells, as with lymphosarcoma and multiple myeloma, respectively.

The diagnostic approach to hypercalcemia should be individualized to the patient; the general approach is summarized in the box on this page.

Differentiating Between Diseases

Differentiating HHM with secondary renal damage from renal failure with secondary hypercalcemia can be a diagnostic challenge. This is especially difficult in patients with marked azotemia and marked hypercalcemia. Differentiation between primary hypercalcemia and primary renal disease is easier when there is a disproportionate elevation in either urea and creatinine or the total serum Ca level. Marked azotemia with mild elevations in the total serum Ca level is more consistent with primary renal disease, and marked hypercalcemia with mild azotemia is more consistent with primary hypercalcemia. Reviewing the history and laboratory work for changes consistent with chronic renal failure, including long-term weight loss, polyuria/polydipsia, and nonregenerative anemia, may help differentiate between primary hypercalcemia and primary renal failure. Unfortunately, many of these clinical findings can also be seen with HHM.

In addition, with HHM, the serum phosphorus (P) value should be low to normal because parathyroid hormone (PTH)–related protein (PTHrP) causes renal Ca reabsorption with phosphorus (P) excretion, whereas, with renal failure, the serum P level is often elevated. The ionized Ca level, when available, is valuable for differentiating the two conditions: With renal failure, the ionized Ca level is usually normal to low, whereas with HHM, the ionized Ca level is increased. Additionally, with appropriate therapy and diuresis, azotemia usually normalizes more rapidly with HHM than with chronic renal failure.

Diagnostic Evaluation of Hypercalcemia

Indicated in most patients

- Complete history (including possible exposure to vitamin D)
- Physical examination (with rectal palpation in dogs)
- Complete blood cell count/serum chemistry panel/urinalysis (confirm that hypercalcemia is real)
- Thoracic and abdominal radiographs
- Fine-needle aspiration cytology on palpable lymph nodes

Usually indicated if initial testing is nondiagnostic

- Abdominal ultrasonography, with aspirates of liver, spleen, and enlarged lymph nodes
- Bone marrow aspiration and bone core biopsy
- PTH, ionized Ca, PTHrP, and calcidiol serology

Indicated in uncommon, specific circumstances

- Adrenocorticotropic hormone stimulation test
- Therapeutic trial with steroids or chemotherapeutic agents

Additional Testing

More specialized diagnostic tests available to confirm or solidify a diagnosis of HHM measure PTH, PTHrP, ionized Ca, and calcidiol levels.[1,2,b] Newer PTH assays that measure intact PTH are much improved over older assays that evaluated either the C-terminal or mid-molecule PTH only.[1,2,9] The major disadvantages of these additional tests in regular practice include high costs, specialized sample handling and shipping requirements, and a slow turnaround time. Therefore, a standard diagnostic investigation for the presence of cancer is usually indicated before sample submission for the more specialized diagnostic tests.

Occasionally, obtaining an etiologic diagnosis with HHM can be difficult. This is especially true when lymphosarcoma is suspected in the absence of peripheral or abdominal lymphadenopathy and aspiration cytology of lymph nodes, liver, spleen, bone marrow, and suspected mediastinal tumors is inconclusive. In these cases, PTH, PTHrP, ionized Ca, and calcidiol levels can be very helpful in securing a diagnosis of HHM[1,2] (Table 1).

Diagnosis Based on Therapeutic Response

Deterioration of the patient secondary to resistant or profound hypercalcemia may dictate the need for diagnosis based on response to therapy while awaiting a serologic diagnosis.[6,11] In these cases, a trial of glucocorticoids or other chemotherapeutic drugs (e.g., L-asparaginase) may help diagnose HHM.[1] A positive response (decreased total and/or ionized Ca values) to L-asparaginase is more specific than a similar response to glucocorticoids

[b]Animal Health Diagnostic Laboratory, Michigan State University, East Lansing.

Table 1. Serum Ionized Ca, PTH, PTHrP, and Calcidiol Values for Differentiating Between Various Causes of Hypercalcemia

Disease	*Ionized Ca Value*	*PTH Value*	*PTHrP Value*	*Calcidiol Value*
HHM	High	Low	High	Normal to high
Primary hyperparathyroidism	High	Normal to high	Low	Normal to high
Vitamin D toxicosis	High	Low	Low	Normal to high
Renal disease	Low to normal	High	Low	Low

because glucocorticoids can improve abnormal Ca homeostasis of numerous causes, including vitamin D toxicosis, hypoadrenocorticism, granulomatous disease, lymphosarcoma, and multiple myeloma.[1,2,10–14] Therapeutic trials with either corticosteroids or chemotherapeutic agents should be considered only after a complete workup and exhaustion of all available diagnostic methods. Sufficient samples required for further testing (e.g., PTH, PTHrP, and calcidiol levels) must be collected before initiating any therapy that might alter results.

TREATMENT

Treatment of HHM can be divided into specific and supportive therapies. Specific treatments are aimed at addressing the underlying cause of hypercalcemia (e.g., treating the malignancy) and are not addressed further in this article. Supportive therapy is directed at decreasing the magnitude of hypercalcemia until an etiologic diagnosis can be made or surgical, chemotherapeutic, or radiation therapy can be safely implemented. In general, supportive therapy is only temporary or partially effective until the underlying cause is identified and treated.

Fluid Therapy

Fluid therapy is the mainstay of the initial supportive treatment of HHM. Administering IV fluids to correct dehydration and promote diuresis helps decrease hypercalcemia secondary to hemoconcentration and promotes calciuresis. Physiologic saline (0.9% sodium chloride [NaCl]) is the fluid of choice because it is devoid of Ca, has a higher concentration of sodium (Na) to promote diuresis,[1,4,11] and lacks the lactate in lactated Ringer's solution. Administering lactated Ringer's solution has been shown to exacerbate the hyperlactatemia often found in dogs with lymphosarcoma.[15] Dehydration should be corrected over 6 to 8 hours followed by volume expansion and diuresis (minimum of 1.5 to 2 times maintenance (100 to 130 ml/kg/day).

Minimum monitoring standards for patient hydration during aggressive IV fluid administration should include twice-daily packed cell volume and total protein readings and frequent body weight determinations. Weight gain or loss after rehydration or decreases or increases in packed cell volume or total protein level could suggest overhydration or dehydration of the patient, respectively. In patients prone to overhydration (e.g., those with congestive heart failure either from preexisting cardiovascular disease or secondary to hypercalcemia), auscultation of the lungs for crackles (suggesting pulmonary edema) every few hours is recommended, preferably in conjunction with monitoring central venous pressure (the method of choice) or urine production (via an indwelling urinary catheter). An increase in central venous pressure of 5 cm H_2O over baseline values (or >12 cm H_2O total) or a urine volume that is less than the fluids administered (after rehydration and accounting for insensible losses) may signal the need to decrease the fluid administration rate. The patient's acid–base status and renal and electrolyte values should be checked twice daily or as dictated by the patient's status and progression and owner's finances.[1,2,6,14,16,17]

The necessity to augment fluid therapy for hypercalcemia with other drugs depends on many factors, including the following[1,2,4,11,18,19]:

- **Patient status**—Cardiovascular and neurologic impairment may require more aggressive therapy.
- **Magnitude of hypercalcemia**—A total serum Ca value greater than 16 mg/dl may call for aggressive emergency management in contrast to values of 12 to 13 mg/dl in a well-hydrated patient, which may call for minimal or no supportive care.
- **Ca × P product**—A product of over 60 increases concerns of soft tissue mineralization.
- **Rate of change in the Ca value**—Rapid increases of 2 to 3 mg/dl may require more aggressive therapy.
- **Duration of hypercalcemia**—Acute, significant elevations in the total serum Ca level, especially to values in excess of 16 mg/dl, may also require more aggressive therapy.

Table 2. Therapeutic Options for HHM in Approximate Descending Order of Recommended Administration

Treatment	*Dose/Dosage*	*Indication*	*Comments*
Volume expansion			
0.9% NaCl SC	75–100 ml/kg/day (diuresis dosage)	Mild hypercalcemia	Contraindicated if peripheral edema is present
0.9% NaCl IV	100–125 ml/kg/day (diuresis dosage)	Mild to severe hypercalcemia	Contraindicated with congestive heart failure or hypertension; potassium chloride should be added to the fluid to prevent hypokalemia
Diuretics			
Furosemide	2–4 mg/kg q8–12h IV, SC, or PO	Moderate to severe hypercalcemia	Volume expansion is recommended before drug administration
Glucocorticoids			
Prednisone or prednisolone	1–2 mg/kg q12h PO, IV, or SC	Moderate to severe hypercalcemia	Etiologic diagnosis or sample collection before administration is strongly advised
Dexamethasone	0.1–0.2 mg/kg q12h PO, IV, or SC		
Bone resorption inhibitors			
Salmon calcitonin	4–6 IU/kg SC q8–12h	Moderate to severe hypercalcemia, especially if due to hypervitaminosis D	Response may be short-lived; vomiting may occur
Pamidronate (bisphosphonate)	1.3 mg/kg in 150 ml 0.9% NaCl in a 2-hr IV infusion; can repeat in 1 week	Moderate to severe hypercalcemia	Few reports of use in dogs; high cost; availability may be a problem
Alkalinizing agent			
Na bicarbonate	1 mEq/kg IV slow bolus; may continue at 0.3 × base deficit × wt (kg) per day	Severe hypercalcemia with severe metabolic acidosis	Requires close monitoring of acid–base status and slow IV administration

If HHM persists despite rehydration and volume expansion with 0.9% NaCl, diuretic therapy to promote calciuresis should be initiated. Furosemide (2 to 4 mg/kg IV q12h) promotes calciuresis by inhibiting active reabsorption of chloride in the thick ascending loop of Henle, which leads to decreased renal tubular reabsorption of Ca ions (Ca^{2+}). Thiazide diuretics are contraindicated because they enhance renal tubular reabsorption of Ca^{2+}.[1,2,11,12,18]

Glucocorticoids

Glucocorticoids can be very effective in treating hypercalcemia but should be reserved until an etiologic diagnosis has been made or until all appropriate samples have been collected[1,2,12,14,18] (Table 2). If glucocorticoid therapy is initiated before a definitive diagnosis is made, an etiologic diagnosis will be much more difficult to make, accurate tumor staging may be prevented, and definitive therapy may be delayed.[9] In addition to being cytotoxic to malignant lymphocytes, glucocorticoids are useful in treating hypercalcemia because they decrease the absorption of Ca from the intestines, reduce bone resorption of Ca, and enhance Ca excretion from the kidneys.[1,2,8,12,13] Therefore, a favorable response to glucocorticoid administration is not pathognomonic for HHM.

Additional Therapeutic Measures

In cases of refractory hypercalcemia or while awaiting an etiologic diagnosis, additional therapeutic measures may occasionally be needed to further decrease the magnitude of hypercalcemia. It is important to remember that normalization of the total serum Ca value is not required to protect the body from the pathologic effects of HHM. A drop in the total serum Ca level of 2 to 3 mg/dl can be sufficient, pending etiologic diagnosis and the initiation of a more specific therapy. Therefore, additional therapies beyond fluids, diuretics,

and glucocorticoids are infrequently required in patients with HHM.

Additional therapeutics that may be helpful in addressing refractory severe HHM include salmon calcitonin, Na bicarbonate, and bisphosphonates (Table 2). Salmon calcitonin decreases bone resorption of Ca and potentially promotes calciuresis. The disadvantages associated with the use of salmon calcitonin include high cost, high frequency of administration, and variable response rates.[1,2,8,11,19]

Bisphosphonates have decreased the use and necessity of salmon calcitonin in human medicine and are increasingly being used in veterinary medicine. Bisphosphonates exert their effect by binding to the hydroxyapatite of bones and decreasing osteoclastic activity and function. Pamidronate is the most commonly used bisphosphonate in veterinary medicine.[1,2,19–21]

Na bicarbonate can also be administered for hypercalcemia to help correct metabolic acidosis or to create a mild metabolic alkalosis because pH increases shift some of the ionized Ca into the protein-bound fraction. Additionally, the bicarbonate portion of Na bicarbonate can bind to ionized Ca to form Ca bicarbonate, thereby decreasing the concentration of ionized Ca. The use of Na bicarbonate for significant hypercalcemia may precipitate soft tissue calcification, which may increase morbidity or mortality. Therefore, the risks of Na bicarbonate administration should be weighed against the potential serious complications.

Other therapies that have been mentioned in the literature but that are rarely indicated include mithramycin, Na EDTA, and peritoneal dialysis. Mithramycin is an antineoplastic antibiotic that has hypocalcemic effects. Unfortunately, its use as a hypocalcemic agent is limited by nephrotoxicity, hepatotoxicity, and thrombocytopenia. Na EDTA has also been used to treat hypercalcemia. EDTA chelates ionized Ca to form soluble complexes that are excreted via the kidneys. The usefulness of Na EDTA is limited, however, because it can be nephrotoxic.[1] Peritoneal dialysis with a low Ca dialysate can be effective in treating hypercalcemia, but its use has not been reported in veterinary medicine.[1]

New Approaches

Newer therapeutic approaches that may prove to be useful in the near future may include Ca channel blockers, somatostatin congers, nonhypercalcemic analogs of calcitriol, and Ca receptor agonists.[1] Ca channel blockers, such as verapamil (0.05 to 0.15 mg/kg IV slowly over 5 minutes, then 2 to 10 µg/kg/min constant rate infusion),[22] can be used to temporarily control hypercalcemic effects on the heart while diagnostics and/or other therapeutics are being administered.[1] Somatostatin congers, nonhypercalcemic analogs of calcitriol, and Ca receptor agonists inhibit PTHrP production and are being investigated because they are potentially effective, easy to administer, and safe.[1]

PROGNOSIS

The prognosis for patients with HHM is typically guarded and influenced by the underlying disease, consequences of hypercalcemia, and the high costs associated with treatment. Apocrine gland adenocarcinomas of the anal sac are locally invasive tumors that often invade adjacent soft tissue structures and frequently metastasize to regional lymph nodes, decreasing the opportunity for surgery. Metastasis to distant lymph nodes, however, does not typically occur until late in the disease. Surgical removal of the primary tumor is still recommended and usually results in normalization of Ca and good quality of life until the tumor recurs or metastases progress. Dogs with apocrine gland adenocarcinoma of the anal sac and HHM or metastasis at the time of diagnosis have a median survival time of 6 months compared with normocalcemic dogs, which have a median survival time of 11.5 months.[5]

Recently, HHM secondary to lymphosarcoma has been shown not to have a negative prognostic effect compared with lymphosarcoma with normocalcemia.[23] This is in contrast to an earlier report stating that dogs with lymphosarcoma and HHM had a poorer prognosis than similar dogs with lymphosarcoma but without HHM.[24] Dogs with HHM and lymphosarcoma had a median survival time of 6 months, with 25% of them living longer than 1 year[23] in the more recent report, compared with previously reported median survival times of 112 days for responders and 34 days for nonresponders.[24]

Published survival rates and statistics for cats with HHM are scarce.[23–25] In a case report of two cats with myeloma and HHM, one cat survived for 16 months.[8]

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ARTICLE #5 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. *Choose the best answer* to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium*.

1. Physiologic saline (0.9% NaCl) is the fluid of choice in the initial treatment of HHM because it
   a. is a balanced electrolyte solution.
   b. has an acid pH that helps shift ionized Ca to protein-bound Ca.
   c. is devoid of Ca, has a high concentration of Na to promote diuresis, and lacks lactate, which may promote lactic acidosis.
   d. is hypotonic and promotes cellular rehydration.

2. Augmenting initial therapy of HHM with additional drug therapy is indicated
   a. when neurologic or cardiovascular deterioration of the patient occurs despite therapy.
   b. when the Ca × P product falls below 60 despite therapy.
   c. when the total serum Ca value drops significantly but fails to return to normal with aggressive fluid therapy.
   d. at initial diagnosis because glucocorticoid administration does not hamper the diagnostic tests.

3. Which statement about glucocorticoids is incorrect?
   a. They are cytotoxic to malignant lymphocytes.
   b. They help decrease Ca absorption from the intestines.
   c. They help reduce Ca resorption from the bones.
   d. They help decrease Ca excretion from the kidneys.

4. Which statement regarding differentiating occult HHM from other causes of hypercalcemia is true?
   a. A normal PTH value despite a high ionized Ca level usually rules out primary hyperparathyroidism as the cause of hypercalcemia.
   b. High PTHrP and ionized Ca values with a low PTH value are most consistent with HHM.
   c. A high ionized Ca level with a low PTH level is consistent with renal disease secondary to hyperparathyroidism.
   d. A high PTHrP value is commonly found with renal disease and HHM.

5. Which statement regarding the usefulness and toxicities of additional therapeutics is true?
   a. Na EDTA can be effective in treating HHM because the EDTA chelates the ionized Ca, but its use is limited because it is insoluble and leads to soft tissue mineralization.
   b. Mithramycin, an antineoplastic antibiotic, has limited clinical use because it can be nephrotoxic and hepatotoxic and can cause thrombocytopenia.
   c. Peritoneal dialysis is widely used to treat HHM in veterinary medicine.
   d. The use of Na EDTA is limited by its hepatotoxicity.

6. Which statement regarding the use of bisphosphonates is true?
   a. Bisphosphonates work by binding to the PTH receptor in the proximal renal tubules and decreasing the reabsorption of Ca in the kidneys.
   b. Pamidronate is the most commonly used bisphosphonate in veterinary medicine, but its use may be limited because of high costs and limited availability.

c. Salmon calcitonin has virtually replaced the use of bisphosphonates in human medicine because it can be administered less often, is more reliable, and is more cost-effective.
d. Bisphosphonates are effective in treating HHM because they decrease osteoblast activity and function.

7. Which statement regarding the prognosis of HHM is true?
   a. Because HHM occurs in approximately 80% to 90% of dogs with apocrine gland adenocarcinoma and wide surgical excision is usually curative, monitoring for recurrence of HHM is unnecessary.
   b. The presence of lymphosarcoma with HHM was recently found not to be a negative prognostic factor.
   c. The consequences of hypercalcemia are of limited importance in determining the prognosis of animals with HHM.
   d. During remission, the quality of life associated with apocrine gland adenocarcinoma or lymphosarcoma and HHM is considered poor; therefore, therapy is generally not considered.

8. Which statement regarding formulating the initial diagnostic plan for hypercalcemia is false?
   a. In a stable animal, rechecking the total serum Ca level on a fasted sample is recommended.
   b. Aspiration of palpable lymph nodes should be attempted in a dog with unexplained hypercalcemia.
   c. A rectal examination should be part of a thorough physical examination in a hypercalcemic patient.
   d. Serum sample quality is of little importance in interpreting the total serum Ca value.

9. Which statement regarding differentiating primary hypercalcemia with secondary renal damage from primary renal disease with secondary hypercalcemia is true?
   a. The relative magnitudes of hypercalcemia versus azotemia are not helpful in differentiating the primary cause.
   b. Low to normal serum P is more consistent with primary renal disease because increases in the PTHrP level promotes P retention.
   c. Ionized Ca can be very helpful in differentiating HHM from primary renal disease because it is high in HHM and normal to low in primary renal disease.
   d. Progressive weight loss, long-term polyuria/polydipsia, and nonregenerative anemia are more commonly found in HHM than in primary renal disease.

10. A therapeutic trial with glucocorticoids is indicated in a hypercalcemic patient
    a. when the patient is deteriorating and all pertinent samples have been collected.
    b. at initial presentation because response to glucocorticoids is pathognomonic for HHM.
    c. whenever the total serum Ca value is elevated and the patient has not been fasted and is otherwise healthy.
    d. during initial rehydration and volume expansion.