Endocrine Emergencies in Dogs and Cats

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KEYWORDS

- Diabetic ketoacidosis
- Hyperglycemic hyperosmolar syndrome
- Hypoglycemia
- Insulinoma
- Hypoadrenocorticism
- Pheochromocytoma
- Thyroid storm
- Myxedema coma

KEY POINTS

- Diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, hypoglycemia, insulinoma, hypoadrenocorticism, pheochromocytoma, thyrotoxicosis, and myxedema coma are all examples of life-threatening complications of endocrine disease.
- Success in treatment of endocrine emergencies is contingent on early recognition and treatment.
- Many endocrine diseases presenting emergently have nonspecific signs and symptoms.
- Endocrine crises are often precipitated by concurrent disease, further making early identification difficult.

Endocrine disorders are common problems in dogs and cats. Although typically presenting with chronic, insidious, and slowly progressive signs, there are some instances when endocrine disease can present with life-threatening complications. Diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar syndrome (HHS), hypoglycemia, insulinoma, hypoadrenocorticism, pheochromocytoma, thyrotoxicosis, and myxedema coma are all examples of life-threatening complications of endocrine disease. Success in treatment of endocrine emergencies is contingent on early recognition and treatment. This article concentrates on clinical signs and emergency management of these endocrine crises. The reader is referred to an endocrinology textbook for further information on long-term care and treatment.

DIABETIC EMERGENCIES: DKA AND HHS

DKA and HHS are 2 diabetic crises that require emergency intervention. DKA is identified by presence of hyperglycemia, glucosuria, ketonemia, or ketonuria with a metabolic acidosis as shown by low pH, low bicarbonate, and large negative base excess.
on arterial or venous blood gas (VBG) analysis. The criteria for HHS include severe hyperglycemia, minimal or absent serum or urine ketones, and severe hyperosmolality. (Table 1 gives a summary of diabetic crises.)

DKA and HHS share a common yet divergent pathophysiology. In both, an absolute or relative lack of insulin renders most cells unable to use glucose for energy and promotes gluconeogenesis and glycogenolysis, thus leading to development of hyperglycemia. In addition, hormone-sensitive lipase activity is increased, thus releasing free fatty acids (FFAs) from adipocytes, which can be oxidized by many tissues to make energy. These FFAs are taken up by the liver, where they are made into triglycerides, metabolized via the tricarboxylic cycle to CO₂ and water, or formed into the ketone bodies: acetoacetate, β-hydroxybutyrate, and acetone. In the uncomplicated diabetic, triglyceride production predominates and the small amounts of ketones that are produced are completely metabolized for energy.¹

Progression to DKA or HHS requires both a lack of insulin as well as increasing concentrations of counterregulatory (or stress) hormones, including glucagon, epinephrine, cortisol, and growth hormone. These hormones are secreted in response to a secondary stressor, although the stressor is not always identified. For example, infection, hyperadrenocorticism, pancreatitis, renal failure, neoplasia, and heart failure have all been identified in patients in diabetic crises.²⁻⁶ The hormonal alterations contribute to development of a diabetic crisis in many ways, including stimulating hepatic glycogenolysis and gluconeogenesis, inhibiting insulin activity, potentiating the effects of glucagon and epinephrine on hepatic glycogenolysis and gluconeogenesis, and increasing protein catabolism (which subsequently impairs insulin activity in muscle and provides amino acids for hepatic gluconeogenesis). Together, these factors contribute to the hyperglycemia, osmotic diuresis, and hyperosmolality in these patients.¹

### Progression to DKA

In DKA, the counterregulatory hormones stimulate lipolysis, which increases the amount of circulating FFAs available for ketone formation. Accumulation of ketones causes ketosis. Systemic acidemia, called DKA, develops once the quantity of

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<th>Summary of diabetic crises</th>
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<td>Diagnostic criteria</td>
<td>Hyperglycemia</td>
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<td>Glucosuria</td>
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<td>Ketonemia/ketonuria</td>
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<td></td>
<td>Metabolic acidosis pH &lt;7.3, HCO₃&lt;15 mEq/L</td>
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<tr>
<td>Common clinical signs and symptoms</td>
<td>PU/PD</td>
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<td>Dehydration</td>
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<td></td>
<td>Hypovolemia</td>
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<td>Anorexia</td>
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<td></td>
<td>Vomiting</td>
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<td></td>
<td>Mental depression</td>
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<tr>
<td></td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Ketone (acetone) breath</td>
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<tr>
<td>Common concurrent conditions</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
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<tr>
<td></td>
<td>Hyperadrenocorticism</td>
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<td></td>
<td>Corticosteroid administration</td>
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<td>Hepatomegaly</td>
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ketoacids overwhelms metabolic pathways and buffering systems. Ketoacids cause osmotic diuresis and, coupled with lack of water intake and ongoing losses (eg, vomiting, diarrhea), contribute to the development of dehydration. Prerenal azotemia results as intravascular volume is reduced and this decline in glomerular filtration rate (GFR) causes glucose and ketones to accumulate at an accelerated rate, exacerbating the clinical state. To maintain serum electroneutrality, negatively charged ketoacids are excreted with positively charged ions such as sodium, potassium, magnesium, and calcium, leading to electrolyte deficiencies.\textsuperscript{1}

**Progression to HHS**

The pathogenesis of HHS is similar to that of DKA, except that in HHS, it is thought that the presence of small amounts of insulin and hepatic glucagon resistance inhibit lipolysis, thereby preventing ketosis.\textsuperscript{7,8} Lower concentrations of growth hormone have also been documented in patients with HHS.\textsuperscript{8,9} In HHS, the primary result of hormonal alterations is hyperglycemia, which promotes osmotic diuresis, thus leading to a vicious circle of progressive dehydration and hyperosmolality. To achieve the magnitude of hyperglycemia that is seen in HHS, a reduction in GFR is required, because otherwise there is no maximum rate of glucose loss via the kidney.\textsuperscript{10,11} (All glucose that enters the kidney in excess of the renal threshold is excreted in the urine in a normal animal). An inverse correlation exists between GFR and serum glucose in diabetics.\textsuperscript{10} Renal failure and congestive heart failure (CHF) are common in cats with HHS and they can also exacerbate the hyperglycemia as a result of their reduction of GFR.\textsuperscript{3} Human HHS survivors have also shown a reduced thirst response, despite increasing vasopressin levels, which may also contribute to dehydration and decreased GFR.\textsuperscript{12}

**Clinical Signs and Symptoms**

Both DKA and HHS may be identified in new or previously diagnosed and treated diabetics. Polyuria (PU), polydipsia (PD), polyphagia, and weight loss are consistent with a diagnosis of diabetes mellitus (DM). PU and PD develop when the magnitude of hyperglycemia exceeds renal threshold, and an osmotic diuresis ensues. Decreased glucose transport into the satiety center is perceived as starvation, and the patient often develops a ravenous appetite. Weight loss occurs as adipose tissue is broken down to provide energy for cells, because their normal energy source, glucose, is unavailable.

The onset of DKA is typically accompanied by lethargy, mental depression, anorexia, vomiting, diarrhea, weakness, and other signs consistent with comorbid disease. Onset of HHS is often associated with hyporexia, lethargy, vomiting, and weakness. In addition, some owners report a history of heart or renal disease or recent-onset neurologic signs, such as circling, pacing, mentation changes, or seizures.\textsuperscript{2–6}

**Physical examination**

Physical examination findings in DKA and HHS can vary with the severity and chronicity of the syndrome and any concurrent diseases. Either condition can present as hypovolemic shock, with or without hypotension. In the typical patient with DKA, dehydration, thin body condition, mental depression, weakness, vomiting, and ketone (acetone) breath are common findings.\textsuperscript{2–6} In HHS, dehydration is typically severe, and neurologic abnormalities, including depression (most common), obtundation, stupor, or coma, may be present. Weakness, ataxia, abnormal pupillary light reflexes, or seizure activity may also be noted.\textsuperscript{5} Neurologic signs are believed to develop secondary to cerebral dehydration induced by severe hyperosmolality.
**Diagnosis**

Clinically ill diabetic animals warrant a full diagnostic evaluation, including a complete blood count (CBC), chemistry, VBG, urinalysis (including ketone measurement), urine culture, and imaging. Clinicopathologic abnormalities vary with underlying disease process and are not specific for DKA or HHS. Anemia, hemoconcentration, and stress or inflammatory leukograms may be seen. Likewise, azotemia, hyperphosphatemia, increased liver enzyme activities, and electrolyte deficiencies may be seen with both diabetic crises. Hyperbilirubinemia, hypercholesterolemia, and hypertriglyceridemia are more common in cats with DKA than those with HHS. Although it is not possible to differentiate HHS from DKA based on the severity of metabolic acidosis, VBG quantifies the degree of acidemia resulting from ketoacids, lactate, and uremic acids. The presence of ketones should be identified by measuring urine or serum ketones using a urine dipstick or point-of-care blood ketone meter.

Profound electrolyte abnormalities may be seen with both DKA and HHS. Although the total body content of potassium is reduced, patients with DKA and HHS may initially have normal or increased blood concentrations as a result of acidosis, severe hyperosmolality, insulin deficiency, or poor renal perfusion. Potassium levels decline with therapy as acidosis improves and as insulin drives glucose and potassium into cells. Serum sodium level may also be misleading, because severe hyperglycemia pulls water into the vasculature and dilutes the serum sodium level, causing a pseudohyponatremia. As the glucose level decreases, the sodium level increases. The true corrected sodium level can be estimated by the following equation:

\[ \text{Na}^{+}_{\text{corr}} = 1.6 \times (\text{measured glucose} - \text{normal glucose})/100 + \text{Na}^{+}_{\text{measured}}. \]

Additional diagnostics such as thoracic and abdominal radiographs, abdominal ultrasonography, thyroid levels, and other endocrine testing, feline leukemia virus/feline immunodeficiency virus, heartworm testing, and echocardiogram may be indicated based on clinical findings and suspected underlying disease processes.

**Emergency Management of Diabetic Crises**

Goals of therapy for patients with HHS and DKA are to (1) replace dehydration deficit and vascular volume, (2) manage electrolyte abnormalities, (3) initiate insulin therapy to help reduce glucose levels and reverse ketone production in DKA, and (4) treat underlying diseases.

**Fluid therapy**

In hypovolemic patients, intravenous (IV) shock fluid therapy should be initiated using a replacement crystalloid. Once the patient is volume resuscitated, the fluid plan should account for the dehydration deficit, ongoing losses, and maintenance needs. A buffered isotonic replacement crystalloid (eg, lactated Ringer’s solution [LRS, Baxter Healthcare Corp, Deerfield IL], Normosol-R, Hospira, Lake Forest, IL LRS, Braun Medical Inc, Irvine CA) is a good initial choice for most patients. The use of fluid therapy alone aids in reduction of blood glucose concentration via dilution and by increasing GFR, which enhances urinary glucose excretion.

Treating a patient with HHS and concurrent CHF presents a dilemma, because IV fluids may exacerbate heart failure. Rehydration must be performed more slowly and cautiously. Nasoesophageal tubes offer an effective means of rehydration, with less risk of volume overload. Specific cardiac therapy is dependent on the type of underlying cardiac dysfunction. A positive inotrope (eg, dobutamine, medium-dose dopamine) or inodilator (ie, pimobendan) may also be indicated to improve cardiac output and perfusion of the kidneys.
Managing electrolytes
Potassium, magnesium, and phosphorus deficiencies should be treated before initiating insulin therapy, because insulin causes rapid decline in these electrolytes as they are driven into cells or are consumed to make energy via glycolysis. Severe electrolyte deficiencies may precipitate life-threatening complications or death. Once these 3 electrolytes are within reference range, insulin therapy may begin (see later discussion). Again, electrolyte levels may decline rapidly with insulin therapy, and deficiencies commonly develop, even if these electrolyte levels are normal or elevated at the time insulin is begun. This finding is particularly true in patients with DKA. Therefore, electrolytes should be monitored frequently (every 6–8 hours initially) and fluids and electrolyte content should be altered appropriately. Hypernatremia should be corrected slowly, with a decrease of no more than 0.5 to 1 mEq/L per hour. Table 2 presents more information on electrolyte supplementation.

Bicarbonate therapy is rarely needed to treat diabetic crises. Bicarbonate therapy administered before potassium replenishment may be detrimental and potentially life-threatening, because it further exacerbates hypokalemia as hydrogen ions moving out of cells to buffer the bicarbonate are exchanged for potassium. Sodium bicarbonate administration can also cause hypernatremia, hyperosmolality, or paradoxical central nervous system (CNS) acidosis, leading to depression, stupor, coma, or death. Bicarbonate therapy is generally reserved for those patients with severe acidemia.

### Table 2
Electrolyte supplementation guide for diabetic crises

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Form</th>
<th>Dose for Supplementation</th>
<th>Consequence of Severe Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>Potassium chloride</td>
<td>20–80 mEq K+/L of fluids</td>
<td>Hypotension, arrhythmias, weakness, cervical ventroflexion, hypoventilation</td>
</tr>
<tr>
<td></td>
<td>(dependent on serum potassium concentration) up to a maximum rate of 0.5 mEq/k*g/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Potassium phosphates (sodium phosphate also available)</td>
<td>0.01–0.2 mmol/kg/h or give 25% of potassium supplementation (see KCl, above) as K-Phos and 75% as KCl</td>
<td>Hemolysis, weakness, obtundation</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium sulfate</td>
<td>0.75–1 mEq/kg given as CRI over 24 h</td>
<td>Refractory hypokalemia, hypotension, obtundation, seizures, weakness, arrhythmias</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Sodium bicarbonate</td>
<td>Rarely needed as the acidemia corrects with fluid therapy and reversal of ketosis. Slowly give one-quarter to one-third of the following: mEq of bicarbonate required = 0.3 × body weight in kg × (desired plasma bicarbonate mEq/L – measured plasma bicarbonate mEq/L)</td>
<td>Severe acidemia can cause hypotension, arrhythmias, neurologic manifestations</td>
</tr>
</tbody>
</table>
(pH <7.1, bicarbonate <8 mmol/L) and signs consistent with severe metabolic acidosis such as refractory hypotension, arrhythmias, and presence of stupor or coma.

**Insulin therapy**

Insulin therapy should not begin until the patient’s hypovolemia is corrected and the dehydration and electrolytes are improved, typically after at least 4 to 6 hours. In addition, serum potassium levels should be at least 3.5 mmol/L before initiation of insulin. The goals of insulin therapy for the patient with DKA are to slowly decrease blood glucose levels and to inhibit further lipolysis and ketogenesis. The use of long-acting insulin is not recommended in the emergent or critically ill patient with DKA or HHS. Instead, regular insulin (Humulin R, Eli Lilly and Co, Indianapolis IN) should be administered using either an intermittent intramuscular (IM) or IV continuous rate infusion (CRI) protocol (Table 3). Use of lispro insulin (Humalog, Eli Lilly and Co, Indianapolis IN) has also been described for treating 6 dogs with DKA. Subcutaneous injections of insulin should not be given, because absorption may be poor or unpredictable in a dehydrated or hypotensive patient. Insulin is less critical for reversal of HHS, because much of the syndrome can be improved just by addressing fluid deficit and GFR. Insulin doses should be reduced by 50% when treating HHS; this facilitates a slow decline in blood glucose and prevents cerebral edema, which could occur because of rapid decline in blood glucose concentration. With both DKA and HHS protocols, the goal is to decrease the glucose levels by no more than 50 to 75 mg/dL/h. Blood glucose should be measured every 2 to 4 hours and the insulin dose adjusted to achieve the

<table>
<thead>
<tr>
<th>Insulin Protocol Type</th>
<th>Initial Dose for DKA</th>
<th>Initial Dose for HHS</th>
<th>Subsequent Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent IM</td>
<td>0.2–0.25 U/kg of regular insulin, then 0.1 U/kg every 2–4 h</td>
<td>0.1 U/kg of regular insulin, then 0.05 U/kg every 2–4 h</td>
<td>Check blood glucose every 4 h. Goal is to reduce blood glucose by 50–70 mg/dL/h. Subsequent insulin doses are increased or decreased by ~25% to meet this goal. Add dextrose to fluids when glucose &lt;250 mg/dL.</td>
</tr>
<tr>
<td>IV regular insulin CRI</td>
<td>Dilute 1.1 U/kg (cat) to 2.2 U/kg (dog) of regular insulin in 250 mL 0.9% NaCl. Start this solution at 10 mL/h</td>
<td>Dilute 0.5 U/kg (cat) to 1.0 U/kg (dog) of regular insulin in 250 mL 0.9% NaCl. Start this solution at 10 mL/h</td>
<td>Check blood glucose every 2 h and adjust CRI rate as necessary (see Table 4)</td>
</tr>
<tr>
<td>IV lispro insulin CRI</td>
<td>Dilute 2.2 U/kg lispro insulin in 250 mL 0.9% NaCl. Start the solution at 10 mL/h</td>
<td>Use of lispro has not been described for treating HHS</td>
<td>Use of lispro insulin has been reported in only 6 dogs with DKA. Check blood glucose every 2 h and adjust CRI rate as necessary (see Table 4)</td>
</tr>
</tbody>
</table>

**Table 3**  
**Insulin protocols for DKA and HHS**

**Abbreviation:** IV, intravenous.
desired rate of decline (Table 4 outlines blood glucose monitoring and insulin dose adjustments).

**Postcrisis Therapy for DM**

Regular insulin protocols should be continued until the animal is eating, at which time the patient is moved to a long-acting insulin such as NPH (neutral protamine Hagedorn [Humulin NPH, Eli Lilly and Co, Indianapolis IN]), protamine zinc (ProZinc, Boehringer Ingelheim Vetmedica Inc, St Joseph MO), or glargine (Lantus, Sanofi-aventis, Bridgewater, NJ). Additional long-term DM therapy should include dietary management and routine patient monitoring. Attentive monitoring, diligent treatment of DM, and diagnosis and treatment of any concurrent diseases are imperative to prevent DKA recurrence.

**Prognosis**

The prognosis for DKA depends on the severity of the acidemia, the type and severity of underlying disease, and the financial limitations of the pet owner, as well as their long-term commitment to treating a diabetic pet. The death and euthanasia rate for veterinary patients with DKA has been reported to be 7% to 30%. In 1 study, azotemia, metabolic acidosis, and hyperosmolality were more severe in cats that died. In dogs, nonsurvivors had lower ionized calcium concentration, hematocrit, and venous pH. Base deficit was associated with outcome, such that each 1 mEq/L increase in base deficit yielded a 9% increase in likelihood of discharge from the hospital. Recurrence rates for DKA in dogs and cats are reportedly as high as 42%.

HHS tends to have a higher mortality, because of the severity of the metabolic derangement and underlying diseases. No clear prognostic indicators have been identified in dogs and cats. Cats with HHS reportedly have a survival to discharge of 35.3% but a long-term survival (>2 months) of only 12%.

**HYPOGLYCEMIA CAUSED BY EXOGENOUS OR ENDOGENOUS INSULIN EXCESS**

Blood glucose concentration is maintained by a balance between insulin and glucagon, cortisol, epinephrine, and growth hormone. When glucose use exceeds glucose production, hypoglycemia ensues. Causes of hypoglycemia can be broadly divided into (1) excess insulin or insulinlike substances, (2) excess glucose use, and (3) decreased glucose production (Box 1). Artifactual or spurious measures caused by improper sample handling or glucometer inaccuracy should also be ruled out.

**Exogenous Insulin Overdose**

Overdoses of exogenous insulin are commonly administered to diabetic pets. These overdoses can occur when insulin is administered in quantities greater than prescribed,

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>Insulin CRI Rate (mL/hr)</th>
<th>Maintenance/Replacement Fluid Composition</th>
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<tbody>
<tr>
<td>&gt;250</td>
<td>10</td>
<td>As is</td>
</tr>
<tr>
<td>200–250</td>
<td>7</td>
<td>plus 2.5% dextrose</td>
</tr>
<tr>
<td>150–199</td>
<td>5</td>
<td>plus 2.5% dextrose</td>
</tr>
<tr>
<td>100–149</td>
<td>5</td>
<td>plus 5% dextrose</td>
</tr>
<tr>
<td>&lt;100</td>
<td>0</td>
<td>plus 5% dextrose</td>
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when the prescribed dose is higher than the animal needs, or when the patient is hypo-
rexic and the insulin dose is not reduced. Exogenous insulin overdose should be sus-
ppected in any hypoglycemic diabetic patient receiving insulin.

**Insulinoma**

Insulinoma is a functional insulin-secreting tumor of pancreatic β cells. Most com-
monly, the tumor is an adenocarcinoma. Insulinomas are most common in middle-
aged to older larger breed dogs, although many breeds are affected. There is no
apparent gender predilection. Insulinomas have also been reported in cats, albeit
rarely.23–26

**Clinical Signs and Symptoms**

Glucose is the obligate energy source for the brain and enters the brain by a concen-
tration gradient-dependent facilitated diffusion. Clinical signs are both neurologic,
caused by neuroglycopenia (cerebral hypoglycemia), and systemic, caused by cate-
cholamines released in response to the hypoglycemia. Chronic hypoglycemia can
cause hypoglycemic unawareness (lack of clinical signs) as a result of upregulated ce-
rebral glucose uptake. Clinical signs are typically episodic and may be precipitated by
fasting, excitement, or exercise.

**Diagnosis**

The diagnosis of an insulinoma, although rare, should be suspected when hypoglyce-
mia is the only or the major finding in an animal with consistent clinical signs

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**Box 1**

**Differentials for hypoglycemia**

- *Excess insulin or Insulin-like Factors*
  - Exogenous insulin overdose
  - Insulinoma and other neoplasia
  - Toxins (eg, xylitol, ethanol) and medications (eg, sulfonylureas, β-blockers)

- *Excess Glucose Utilization*
  - Infection (eg, sepsis, Babesia)
  - Pregnancy
  - Paraneoplastic syndrome
  - Extreme exercise (hunting dog) or seizures

- *Reduced Glucose Production*
  - Neonates
  - Hepatic dysfunction (eg, portosystemic shunt, hepatitis, lipidosis, cirrhosis, storage diseases)
  - HA
  - β-Blockers
  - Deficiencies of glucose regulating hormones or enzymes
  - Spurious
  - Polycythemia or leukocytosis
  - Collection or storage problems
(eg, lethargy, malaise, collapse, weakness, vomiting, tremors, seizures). Blood work is typically normal aside from hypoglycemia. Nonspecific increases in liver enzyme activities and hypokalemia caused by insulin driving potassium into cells may also be seen.23–26

Insulinoma is confirmed by identifying a normal or increased insulin concentration on a blood sample taken during a hypoglycemic episode (glucose <60 mg/dL). For patients with episodic hypoglycemia, a supervised fast or multiple blood glucose checks may be necessary to identify hypoglycemia. If insulin levels are equivocal, a calculated amended insulin/glucose ratio (AIGR) <30 mg/dL suggests insulinoma: AIGR = (insulin × 100) ÷ (plasma glucose – 30). Use of the ratio has fallen out of favor, because patients with other causes of hypoglycemia can also have an abnormal ratio.24,25 Performing the test on at least 4 samples may improve the sensitivity of the test.27 In addition, low fructosamine concentrations, which reflect the blood glucose concentration over the previous 1 to 2 weeks, have also been identified in dogs with insulinoma.28–30 Provocative testing such as the glucagon tolerance test, oral glucose tolerance test, tolbutamide tolerance test, and epinephrine stimulation test have been tried but are no more sensitive than other tests and may precipitate hypoglycemia.26

Thoracic radiographs and abdominal ultrasonography are used to look for evidence of metastatic disease. Abdominal ultrasonography is also used to try to identify a mass in the pancreas, although it is not a particularly sensitive method and failure to identify a mass does not rule out the presence of insulinoma.31 Computed tomography, magnetic resonance imaging, and scintigraphy can also be considered as diagnostic aids.31 Surgical exploration may be used in an attempt to identify the insulinoma.

Emergency Management of a Hypoglycemic Crisis

For symptomatic hypoglycemic patients, the most rapid and effective treatment is dextrose (0.5–1 mL/kg of 50% dextrose, diluted, IV). However, in animals with suspected or confirmed insulinomas, boluses of dextrose should be used with caution, because they may stimulate release of more insulin from the tumor, leading to a vicious cycle of dextrose bolus followed by rebound hypoglycemia. An infusion of dextrose may be tried in lieu of or after a bolus to maintain blood glucose concentration. Dextrose infusions are formulated by adding 50% dextrose to a maintenance or replacement crystalloid solution, typically to make a final dextrose concentration of 2.5% to 5% (add 50–100 mL of 50% dextrose to a 1-L bag of crystalloids). Dextrose infusion may need to be continued for hours to days after exogenous insulin overdose, depending on the type of insulin and magnitude of the overdose. Once the patient is able to eat, small frequent meals that are low in simple carbohydrates and high in protein, fat and complex carbohydrates help maintain euglycemia. Blood glucose should be monitored every 2 to 4 hours to ensure adequate and not excessive supplementation and determine when it is possible to taper off the dextrose infusion.

Glucocorticoids, such as prednisone or dexamethasone, antagonize insulin effects and stimulate gluconeogenesis, and this may help stabilize the blood glucose concentration in the patient with an insulinoma. An infusion of glucagon is also an effective method for treating animals with refractory hypoglycemia caused by insulinoma or exogenous insulin overdose.32 Table 5 presents information about dosing.

The goal of emergent therapy is to eliminate clinical signs of hypoglycemia; it may not be necessary or even possible to return the glucose to reference range. Neuroglycopenic symptoms should resolve or markedly improve within a few minutes of resolution of the hypoglycemia; although prolonged, severe neuroglycopenia can cause irreparable neuronal damage.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
<th>Indication/Mechanism of Action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Dog: 0.1–0.4 mg/kg by mouth every 12–24 h</td>
<td>For chronic management of hypertension Calcium channel blocker, arterial vasodilator</td>
<td>Start low and titrate upwards, if needed In dogs, often used in conjunction with angiotensin-converting enzyme inhibitor for managing chronic hypertension</td>
</tr>
<tr>
<td></td>
<td>Cat: 0.625–1.25 mg per cat by mouth every 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>Dog: 0.25–1 mg/kg by mouth every 12 h</td>
<td>For control of arrhythmias in hyperthyroid storm, possibly in pheochromocytoma Selective $\beta_1$-blocker</td>
<td>In pheochromocytoma, use only after complete $\alpha$ receptor blockade or could precipitate hypertensive crisis</td>
</tr>
<tr>
<td></td>
<td>Cat: 6.25–12.5 mg per cat by mouth every 12–24 h</td>
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<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.1–0.5 mg/kg IV as initial dose, then 0.05–0.1 mg/kg IV every 12 h</td>
<td>Antagonizes insulin, increases blood glucose in hypoglycemia Glucocorticoid supplementation for HA</td>
<td>Does not interfere with cortisol assay Doses up to 2.0 mg/kg have been reported; this is likely excessive because it is equivalent to $\sim$ 14 mg/kg prednisone</td>
</tr>
<tr>
<td>Dextrose</td>
<td>Bolus: 0.5–1 mL/kg of 50% dextrose (diluted), followed by CRI of 2.5%–5% dextrose (or more) as needed in fluids</td>
<td>Provides source of glucose to treat hypoglycemia Stimulates insulin secretion in hyperkalemia</td>
<td>Avoid dextrose bolus in patients with suspected insulinoma Solutions $&gt;5%$ are ideally administered via central line</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Start with 5 mg/kg by mouth twice daily; increase as needed to a maximum of 30 mg/kg by mouth twice daily to control clinical signs</td>
<td>Inhibits pancreatic insulin secretion For chronic medical management of insulinoma</td>
<td></td>
</tr>
<tr>
<td>Desoxycorticosterone pivalate (DOCP)</td>
<td>Start with 2.2 mg/kg IM or subcutaneously every 25 d. Titrate subsequent dose and interval based on electrolyte monitoring</td>
<td>Mineralocorticoid replacement for HA For chronic therapy. Give with prednisone because has no glucocorticoid activity Must not be given IV</td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>CRI of 10–200 $\mu$g/kg/min Can be preceded by loading dose of 0.25–0.5 mg/kg IV over 2 min</td>
<td>Selective $\beta_1$-blocker For control of arrhythmias in thyroid storm, possibly in pheochromocytoma</td>
<td>In pheochromocytoma, use only after complete $\alpha$ receptor blockade or could precipitate hypertensive crisis</td>
</tr>
<tr>
<td>Medication</td>
<td>Dosing Instructions</td>
<td>Indications</td>
<td>Notes/Additional Information</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fludrocortisone (Florinef)</td>
<td>Start at 0.01 mg/kg by mouth every 12 h, titrate upwards every 1–2 wk as needed (based on electrolytes) until stable</td>
<td>For HA: provides both mineralocorticoids and glucocorticoid</td>
<td>Patient may or may not also require routine daily prednisone</td>
</tr>
<tr>
<td>Furosemide</td>
<td>1–4 mg/kg IV every 1–2 h during crisis or 0.66 mg/kg/h as CRI</td>
<td>Loop diuretic for treating pulmonary edema in heart failure, may be needed to treat patients with thyroid storm with secondary CHF</td>
<td>Chronic therapy: start 2 mg/kg by mouth every 12 h (dogs) or 6.25 mg/cat by mouth every 12–24 h (cats) adjusted as needed to control edema</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Bolus 50 ng/kg IV followed by CRI of 5–10 ng/kg/min (up to 40 ng/kg/min) to effect</td>
<td>For acute management of hypoglycemic crisis caused by insulinoma or insulin overdose. Stimulates glycogenolysis and gluconeogenesis</td>
<td>Reconstitute based on manufacturer’s instructions to a 1000-ng/mL solution</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>0.3–0.5 mg/kg/h as IV infusion for a few hours or give 2–4 mg/kg IV every 8 h</td>
<td>Glucocorticoid with mild mineralocorticoid effects, for use in acute hypoadrenal crisis</td>
<td>Use only after ACTH stimulation test has been completed</td>
</tr>
<tr>
<td>Ipodate sodium or calcium</td>
<td>50 mg by mouth every 12 h or 100–200 mg per cat by mouth every 24 h</td>
<td>For reduction of thyroid hormone secretion in hyperthyroid storm Blocks conversion of T₄ to T₃ Blocks T₃ receptors</td>
<td>May be available only from compounding pharmacy</td>
</tr>
<tr>
<td>Methimazole (Tapazole)</td>
<td>Start with 2.5 mg per cat by mouth or to the inner pinna (using transdermal product) every 12–24 h</td>
<td>For treatment of hyperthyroidism, inhibits thyroid hormone synthesis</td>
<td>Treatment of hyperthyroidism decreases GFR, monitor for azotemia</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Start 0.5 µg/kg/min, titrate upwards to desired blood pressure (typically &lt;200 mm Hg, reducing systolic blood pressure by ~25% over 4 h)</td>
<td>For acute hypertensive crisis in thyroid storm or pheochromocytoma Nitrates cause vasodilation independent of catecholamines</td>
<td>Continuous direct or frequent indirect blood pressure monitoring is essential</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Start with 0.25 mg/kg by mouth twice a day, increase dose gradually every few days until signs of hypotension or adverse drug reaction occur up to a maximum dosage of 2.5 mg/kg by mouth every 12 h</td>
<td>For acute hypertensive crisis in thyroid storm or pheochromocytoma α-Blocker</td>
<td>Takes multiple days to reach maximum receptor blockade. Allow 2 wk of therapy before surgery</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
<th>Indication/Mechanism of Action</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Prednisone           | 1. For HA: 0.1–0.22 mg/kg, then taper to lowest dose needed to control clinical signs  
2. For insulinoma: 0.25–0.5 mg/kg by mouth every 12 h | 1. Glucocorticoid supplementation for HA  
2. Antagonize insulin, increases blood glucose in insulinoma | 1. Use only after ACTH stimulation test has been completed  
Prednisolone is preferred for cats |
| Prednisolone         |                                                                           |                                                                                               |                                                                                             |
| Propranolol          | For susceptible arrhythmias: 0.02 mg/kg IV slowly  
Dog: 0.1–0.2 mg/kg by mouth every 8 h  
Cat: 2.5 mg by mouth (up to 10 mg) per cat every 8–12 h | Nonselective β-blocker  
Used to treat arrhythmias in hyperthyroid storm, possibly in pheochromocytoma | In pheochromocytoma, use only after complete α-receptor blockade or could precipitate hypertensive crisis |
| Thyroid hormone      | For myxedema coma: 5 μg/kg (0.005 mg/kg) IV every 12 h during crisis  
For long-term management: 0.02 mg/kg by mouth every 12 h | For thyroid supplementation in dogs with hypothyroidism | Preferentially use IV for hypothyroid crisis/myxedema coma. If IV is unavailable, give orally or via a nasogastric tube |
| (levothyroxine)      |                                                                           |                                                                                               |                                                                                             |

Postcrisis Management of Insulinoma

Surgical excision is the treatment of choice for insulinomas, because it results in the longest survival times. However, metastatic disease is evident at surgery in up to 50% of cases, and occult metastasis is present in most dogs. Thus, surgery is considered a palliative procedure for all animals, even when a single lesion is initially identified. The primary tumor is not always identifiable at surgery. When found, the primary tumor and suspected metastatic lesions should be removed, if possible, and submitted for histopathology.

Medical management for patients not undergoing surgery or those with metastatic disease may include dietary management, glucocorticoids, and chemotherapy. Small, frequent meals that are low in simple carbohydrates and high in protein, fat and complex carbohydrates help maintain euglycemia. Glucocorticoids such as prednisone, hydrocortisone, or dexamethasone (see Table 5) antagonize insulin effects and stimulate gluconeogenesis and are indicated for long-term management of the insulinoma patient. Diazoxide (10–60 mg/kg by mouth divided every 12 hours to effect) inhibits pancreatic secretion, stimulates gluconeogenesis and glycogenolysis, and inhibits cellular uptake of glucose. Chemotherapy with streptozocin (which destroys pancreatic β-cells), octreotide (which suppresses insulin synthesis and release), and alloxan (a β-cell cytotoxic) are also management options.

Prognosis

The prognosis for insulinoma is dependent on extent of disease or metastasis and on management choices. Survival is from 74 days up to a median of more than 3.5 years for dogs undergoing surgery followed by medical management after recurrence.

HYPOADRENOCORTICISM

Hypoadrenocorticism (HA), also called Addison’s disease, is classically a deficiency of cortisol and mineralocorticoids, although isolated cortisol deficiency can also occur. Primary HA occurs secondary to destruction of the adrenal cortex either because of immune-mediated destruction (most common in dogs), neoplasia, infection, hemorrhage, iatrogenic causes (eg, mitotane, trilostane), or hemorrhage. Most patients with HA have deficiencies in both cortisol and mineralocorticoids. Secondary HA is the absence of cortisol, which occurs when the pituitary fails to produce adrenocorticotropic hormone (ACTH), which stimulates adrenal cortisol production. These patients are deficient only in cortisol. Secondary HA is typically caused by destruction or damage to the pituitary such as by neoplasia, trauma, or infection or inflammation. Both tertiary HA, which is lack of corticotrophin-releasing hormone secretion, and isolated mineralocorticoid deficiency are rare.

Cortisol and mineralocorticoids have varied and important functions in the body. The mineralocorticoid aldosterone is part of the renin, angiotensin, aldosterone system, which is activated by hypovolemia, hypotension, and low blood sodium concentration. Aldosterone is vital to maintaining electrolyte concentrations by stimulating sodium and chloride reabsorption and potassium excretion in the cortical collecting duct of the renal tubule. Water follows the sodium and results in expansion of vascular volume. Cortisol is also important for maintaining water balance and vascular volume. Cortisol has multiple effects on the vasculature, including maintaining endothelial integrity, vascular permeability, and sensitivity to catecholamines, thus helping maintain blood pressure. In addition, cortisol helps maintain blood glucose concentration by stimulating gluconeogenesis and lipolysis and antagonizing insulin. Cortisol suppresses inflammation and is trophic for the bone marrow, stimulating erythropoiesis.
HA is most common in young to middle-aged dogs and is rare in cats. Females are affected more often than males, except in certain breeds, in which they are affected with equal frequency. Although dogs of any breed can be affected, certain breeds seem to have an increased risk or genetic predisposition, including Nova Scotia duck tolling retrievers, poodles, Portuguese water dogs, West Highland white terriers, and English springer spaniels.36–38

### Clinical Signs and Symptoms

HA is often called the Great Pretender because the spectrum of clinical signs is nonspecific and can be consistent with multiple other disease processes. Clinical signs can be intermittent or waxing and waning in nearly half of the reported cases. Although most dogs have chronic clinical signs, an acute exacerbation may be precipitated by a stressful event, such as a trip to the groomer or veterinarian, a stay at a boarding facility, or changes in the household.

Clinical signs primarily include lethargy, weakness, PU/PD, and gastrointestinal (GI) signs, including anorexia, vomiting, diarrhea, or abdominal pain. Tremors/shaking, collapse, melena, hematochezia, and hematemesis may also be seen.39,40

Physical examination findings are dependent on the stage of disease and range from simple dehydration to signs of hypovolemic and vasodilatory shock, including muffled heart sounds, weak pulses, prolonged capillary refill time, hypotension, hypothermia, and severe dehydration. These findings are a product of fluid losses from the GI tract, renal water losses that accompany renal sodium wasting, and reduced vascular sensitivity to catecholamines. Dogs with mineralocorticoid deficiency may be bradycardic because of hyperkalemia, and an electrocardiogram may show evidence of this hyperkalemia (eg, blunted or absent P waves, tented T waves, and widened QRS complexes).

### Diagnosis

Attaining a definitive diagnosis of HA requires adrenal testing, although history and routine blood work may provide a high degree of suspicion (Table 6). Electrolyte abnormalities associated with HA include hyperkalemia, hyponatremia, and hypochloremia, although they are not unique to this disorder.40 These abnormalities occur because the aldosterone deficiency prevents normal sodium reabsorption and potassium excretion in the cortical collecting duct. Chloride changes typically accompany and parallel sodium abnormalities.

### Testing for HA

The electrolyte abnormalities give rise to the popular Na/K ratio as a screening test for HA. An Na/K ratio less than 27:1 has a sensitivity of 70% to 89% and specificity of 94% to 97% for HA, whereas lower ratios are more specific for the diagnosis.41,42 A recent study reported that combining Na/K ratio and lymphocyte count was consistently more sensitive and specific when compared with either variable alone, suggesting that this combination may be a good screening test.41 Although most dogs in the study had normal lymphocyte counts, dogs with HA had significantly higher counts (median 2.38 [range 0.80–8.20] \( \times \) 10³ cells/µL) than those without HA (median 1.07 [range 0–6.00] \( \times \) 10³ cells/µL).41

The gold standard for diagnosis of HA remains the ACTH stimulation test. To perform an ACTH stimulation test, a baseline blood sample is obtained, 5 µg/kg (maximum of 250 µg/dog) of synthetic ACTH (cosyntropin) is given IM or IV, and a second sample is taken an hour later; cortisol concentrations are measured on both samples. Dogs with HA have either a severely blunted or absent response to ACTH.
Basal cortisol levels can also be used as a diagnostic tool for HA. In 1 study, basal cortisol lower than 1 μg/dL was 100% sensitive and 98% specific for HA; basal cortisol lower than 2 μg/dL was 100% sensitive but only 78% specific.\(^43\) Ratios of endogenous cortisol/ACTH and aldosterone/renin have been found to provide specific diagnosis of primary hypocortisolism and hypoaldosteronism. Whereas plasma concentrations of these individual hormones overlapped between healthy dogs and dogs with HA, the ratios of endogenous cortisol/ACTH and aldosterone/renin identified each group without overlap.\(^44\)

### Imaging
There are no specific radiographic abnormalities in animals with HA. If thoracic radiographs are taken before completing resuscitation, they may show signs of hypovolemia, including microcardia, reduced pulmonary vasculature size, or small caudal vena cava size.\(^40\) Megaeosophagus has also been reported in dogs with HA.

Abdominal ultrasonography may identify the presence of small adrenal glands. Dogs with HA have significantly thinner adrenal glands than healthy dogs and dogs with non-HA illness. A left adrenal gland that measured less than 3.2 mm thick was highly suggestive of HA in 28 of 29 dogs.\(^45\)

### Emergency Management of HA
Therapy for HA is aimed at reversing the hypovolemia, shock, hyperkalemia, and hypoglycemia and then providing replacement hormones.

### Table 6
**Common clinicopathologic abnormalities in dogs with HA**

<table>
<thead>
<tr>
<th>Clinicopathologic Abnormality</th>
<th>Reasons for Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia, normochromic, normocytic, nonregenerative</td>
<td>Loss of red blood cells via GI hemorrhage; lack of steroids contributes (cortisol stimulates erythroid production)</td>
</tr>
<tr>
<td>Lack of stress leukogram (ie, neutrophil count not increased, may have eosinophilia or lymphocytosis)</td>
<td>Lack of steroids. A stress leukogram is expected in an animal as sick as an Addisonian</td>
</tr>
<tr>
<td>High alanine aminotransferase level</td>
<td>Poor perfusion of liver (shock)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Probably multifactorial: GI losses, decreased synthesis, decreased nutrient intake and absorption</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Cortisol is needed to stimulate gluconeogenesis and glycogen storage. Patients are not typically symptomatic for hypoglycemia</td>
</tr>
<tr>
<td>Hypercalcemia (total), with or without ionized hypercalcemia</td>
<td>Exact mechanism unknown, may be caused by hemoconcentration, decreased GFR, and decreased renal calcium excretion. Resolves with supportive care, no specific therapy required</td>
</tr>
<tr>
<td>Increased blood urea nitrogen (BUN) and creatinine</td>
<td>Dehydration and hypovolemia; increased BUN can also result from GI bleeding</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Decreased renal excretion as a result of dehydration and hypovolemia</td>
</tr>
<tr>
<td>Dilute urine (specific gravity &lt;1.030 in face of azotemia)</td>
<td>Renal sodium wasting</td>
</tr>
</tbody>
</table>
The cause of death for patients with HA is typically the result of hypovolemic shock, so aggressive fluid resuscitation is imperative. A shock bolus (20–30 mL/kg, IV) of a replacement crystalloid such as Normosol-R, LRS, 0.9% NaCl, or Plasmalyte-A, is indicated. Many sources advocate use of 0.9% NaCl (with 154 mEq Na/L) as the preferred resuscitation solution; however, multiple cases of myelinolysis have occurred in dogs with HA that had rapid correction of their hyponatremia.46–48 Several days after the rapid increase in sodium, myelinolysis manifests as neurologic signs, including lethargy, weakness, ataxia, hypermetria, and trouble swallowing, which may take weeks to months to resolve, if at all. A lower sodium resuscitation fluid, such as LRS (with 130 mEq Na/L) may be indicated to prevent this complication. Regardless of fluid chosen, serum sodium should not increase by more than 0.5 mEq/L/h in a patient with chronic hyponatremia, particularly when the initial sodium is 120 mEq/L or lower.

Hyperkalemia associated with HA typically improves with fluid resuscitation alone. However, in patients with life-threatening hyperkalemia (manifesting bradycardia or arrhythmias), more specific, rapidly acting therapy such as calcium gluconate (as a cardioprotective agent) or insulin, dextrose, bicarbonate, or a β-agonist (to lower potassium levels) are indicated.

Table 7 presents more information regarding these therapies.

In conjunction with fluid therapy, supplementation with glucocorticoids is indicated for any animal suspected of having an HA crisis. Glucocorticoids help reduce GI signs and, more importantly, stabilize the vascular volume and blood pressure. Dexamethasone is typically used until the ACTH stimulation is completed, because dexamethasone is not measured in the cortisol assay. Hydrocortisone or prednisone/prednisolone can also be considered once adrenal testing is completed (see Table 5 for more information).

Additional supportive and symptomatic therapy for GI complications such as gastric acid reducers (eg, histamine 2 blockers, proton pump inhibitors), sucralfate, and antiemetics is indicated. For animals with GI hemorrhage, antibiotic coverage (eg, ampicillin, 22 mg/kg IV every 8 hours) may reduce risk of bacterial translocation across the compromised mucosal surface.

Postcrisis Management of HA

Once the patient has been stabilized and the results of the ACTH stimulation have returned, long-term therapy can begin. Glucocorticoid deficiency is typically managed with oral prednisone and titrated to the lowest dose needed; the physiologic glucocorticoid dose needed to control HA is lower than traditional antiinflammatory doses. (See Table 5 for dosing.) Patients usually also need extra supplementation at times of stress, such as during periods of illness, hospitalization, travel, or changes in living conditions.

Mineralocorticoid-deficient patients also require mineralocorticoid replacement; however, the need for supplementation in the midst of the HA crisis is debated. Most patients can be stabilized with intensive fluid resuscitation and glucocorticoids alone; some clinicians prefer to initiate mineralocorticoid therapy during the crisis. Fludrocortisone (Florinef) is a short-acting synthetic glucocorticoid that also has mineralocorticoid activity; it can be given orally or rectally. Desoxycorticosterone pivalate (DOCP, Percorten-V) is a long-acting parenteral mineralocorticoid given IM once per month. (See Table 5 for dosing.) Complications are unlikely if DOCP is administered to a suspected Addisonian that is later determined to have a normal ACTH stimulation test.49 Dogs receiving DOCP usually require concurrent prednisone therapy, whereas those receiving fludrocortisone often do not require daily glucocorticoid supplementation.
Subsequent doses of DOCP are determined by serum sodium and potassium levels 12 days after the first dose; if hyponatremia or hyperkalemia is present, the next dose is increased by 5% to 10%, and vice versa. Electrolytes should be measured again at 25 days; if hyponatremia or hyperkalemia is present, the interval until the next dose is decreased to 24 days. If hypernatremia or hypokalemia is present, the interval until the next dose can be extended to 26 days. These rechecks are continued in this way until the optimal dose is identified, after which rechecks can be extended to 2 to 4 times yearly in otherwise normal, well-controlled animals. For fludrocortisone therapy, electrolytes should be monitored every 1 to 2 weeks initially and therapy should be tailored

### Table 7

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV replacement crystalloid fluids</td>
<td>Many</td>
<td>Dilution of potassium, diuresis</td>
<td>Low concentration of K⁺ in balanced replacement crystalloids should not worsen hyperkalemia</td>
</tr>
<tr>
<td>Calcium gluconate, 10% solution</td>
<td>0.5–1.5 mL/kg over 10–20 min</td>
<td>Rapidly cardioprotective by increasing the threshold potential</td>
<td>Does not lower potassium, protects heart, whereas other methods are used to reduce potassium; monitor electrocardiograph and slow or discontinue infusion if arrhythmias occur</td>
</tr>
<tr>
<td>Regular insulin</td>
<td>0.25–0.5 U/kg IV or IM given with dextrose bolus (4 mL of 50% dextrose IV per unit insulin given)</td>
<td>Insulin stimulates obligate cotransport of glucose and potassium into cells</td>
<td>Rapid onset. Must also supplement dextrose in fluids until insulin effect wears off</td>
</tr>
<tr>
<td>Dextrose</td>
<td>0.5–1 mL/kg bolus followed by CRI of 2.5%–5% dextrose solution</td>
<td>Stimulate endogenous insulin production, also maintains blood glucose after exogenous insulin administration</td>
<td>Also addresses hypoglycemia common with HA</td>
</tr>
<tr>
<td>Albuterol (β-agonist)</td>
<td>Cat: 2 puffs (90 µg/puff) Dog weighing 30 kg (60 lb): 0.5 mL of 0.5% solution nebulized in 4 mL of saline</td>
<td>Cat: Using mask and spacer device, breathe 7–10 s</td>
<td>Best dose for hyperkalemia unknown, this dose is based on asthmatic therapy Dose can be repeated every half an hour for 2–4 h in crisis</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>1–3 mEq/kg over 30 min</td>
<td>Potassium moves into the cell in exchange for hydrogen as pH increases</td>
<td>Slow onset of action</td>
</tr>
</tbody>
</table>
based on results. It is not uncommon for dogs to require steady increases in fludrocortisone dose over the first year or so.

**Prognosis**

With intensive fluid resuscitation followed by committed and attentive follow-up care and hormonal supplementation, most patients with HA live normal lives.40

**PHEOCHROMOCYTOMA**

Pheochromocytoma is an uncommon tumor of the catecholamine-secreting chromaffin cells of the adrenal medulla reported in dogs, cats, and other species. Pheochromocytoma can be malignant or locally invasive and has been reported in a multitude of metastatic sites.50–53 Pheochromocytoma has also been reported in dogs with concurrent hyperadrenocorticism.54

**Clinical Signs and Symptoms**

Clinical signs and physical examination findings associated with pheochromocytoma are often intermittent, because they occur during surges of catecholamine secretion, and include weakness, collapse, tachypnea, tachyarrhythmias, hypertension, and seizures.50–53 Retinal or retroperitoneal hemorrhage and epistaxis have also been reported.55–57 Acute presentation of pheochromocytoma is usually associated with severe hypertension, hemorrhage, or arrhythmias, which require emergent intervention.

Presumptive diagnosis is based on history, clinical signs, and presence of an adrenal mass identified on ultrasonography. Invasion into the caudal vena cava is also frequently reported.51,52,56,58 Plasma and urine catecholamines, metanephrines, and ratios of these (particularly the urine normetadrenaline/creatinine ratio) show promise for diagnosis of pheochromocytoma but are not readily available.59–61 Most often, definitive diagnosis is via histopathology of surgically excised tumors.

**Emergency Management of Pheochromocytoma**

α-blockade using the α1-antagonist phenoxybenzamine reduces hypertension that is the result of catecholamine-mediated vasoconstriction. Because it takes several days for maximal α-blockade, severe hypertension manifesting with neurologic signs, retinal detachment, or hemorrhage requires more rapid intervention. Fast-acting vasodilator drugs such as nitroprusside or hydralazine can be used; both drugs have a rapid onset of action, and nitroprusside can also be rapidly titrated to effect. Other blood pressure-lowering drugs such as amlodipine and benazepril/enalapril do not lower the blood pressure rapidly enough in a crisis but may be useful long-term. In human medicine, magnesium sulfate has been advocated as a treatment of hypertension for patients with pheochromocytoma under anesthesia or in crisis.62,63 Magnesium blocks catecholamine receptors and also inhibits the release of catecholamines from the adrenal medulla and peripheral nerve terminals. Magnesium also causes vasodilation and has some antiarrhythmic properties. There are no data on the efficacy of magnesium for treating pheochromocytoma in veterinary medicine. (See Table 5 for dosing.)

Arrhythmias seen with pheochromocytoma may include atrial tachycardia, ventricular premature contractions, ventricular tachycardia, and atrioventricular block. Use of β-blockers to treat arrhythmias should be avoided until α-blockade is in full effect. Early β-blockade prevents β2-mediated vasodilation, thus leaving α-mediated vasoconstriction unopposed and possibly precipitating a hypertensive crisis. Magnesium may be useful in treating pheochromocytoma-induced arrhythmias.62 Depending on
the type of arrhythmia, lidocaine, procainamide, and diltiazem can be tried if arrhythmias are ongoing and life-threatening. Severe retroperitoneal hemorrhage or epistaxis may require shock fluid therapy to restore circulating volume and red blood cell transfusions to improve blood oxygen content.

Postcrisis Management of Pheochromocytoma

Surgical excision of the tumor is the treatment of choice, although perioperative morbidity and mortality can be high.\textsuperscript{50–52} Hypertension, hypotension, extreme tachycardia, and arrhythmias have all been documented during surgery and anesthesia for pheochromocytoma excision. Dogs treated with phenoxybenzamine for 2 weeks before surgery had decreased mortality compared with dogs that were not pretreated with phenoxybenzamine (13% vs 48%, respectively).\textsuperscript{50} Other factors associated with increased mortality in 1 or more studies include longer surgical time, intraoperative arrhythmias,\textsuperscript{50} large tumors, and acute adrenal hemorrhage.\textsuperscript{64}

HYPERTHYROIDISM: THYROTOXICOSIS AND THYROID STORM

Hyperthyroidism in the cat is typically the result of a functional thyroxine (T\textsubscript{4})-secreting thyroid adenoma. Less commonly, cats and dogs present with functional thyroid adenocarcinomas. Thyroid storm (TS) is a rare, acute exacerbation of thyrotoxicosis marked by fever and CNS, cardiovascular, and GI or hepatic signs. This constellation of clinical signs is well recognized in human medicine as TS. TS is a less well-described entity in veterinary medicine, although feline hyperthyroid crises often include 1 or more of these abnormalities.

What causes an animal to progress from being hyperthyroid to TS is not clear. As in other endocrinopathies, there is believed to be a catalyst, although it is not always recognized. Infections, other endocrinopathies, concurrent diseases, and antithyroid treatments, including radioiodine therapy, methimazole, or surgery, may contribute to development of TS. In 1 human study, TS was most common in newly diagnosed hyperthyroid patients, with most cases occurring in the first year of treatment. In addition, TS seemed to be more common in patients who took their antithyroid medications irregularly or stopped taking them altogether.\textsuperscript{65}

The levels of total and free thyroid hormones in patients with TS are not different from those in patients with hyperthyroidism without crisis.\textsuperscript{66,67} It is hypothesized that a rapid change in thyroid level, an alteration in thyroid-binding hormone number or affinity, or an increased sensitivity to catecholamines may contribute to development of TS.\textsuperscript{68}

Clinical Signs and Symptoms

Thyroid hormone is instrumental in function of most tissues in the body and increases metabolic rate and oxygen consumption by most tissues. Clinical signs of thyrotoxicosis in the cat involve the respiratory, cardiovascular, and neurologic systems.

Thyroid hormone increases the number and sensitivity of β-receptors in the heart and acts as a positive inotrope and chronotrope, which may account for some of the cardiovascular signs associated with thyroid excess and TS. Tachycardia, arrhythmias, gallop rhythm, and murmurs may all be identified in thyrotoxic cats. Thyroid hormone also sensitizes the vasculature to catecholamines, contributing to hypertension. Tachypnea, respiratory distress, and abnormal auscultation may be seen as a consequence of heart failure. Hypertension can lead to neurologic signs, including acute blindness from retinal hemorrhage or retinal detachment, seizures, depressed mentation or stupor, and sudden death.\textsuperscript{69,70} Weakness and cervical ventroflexion can be
seen secondary to severe hypokalemia,71 and loss of limb function as a result of thromboembolism has also been reported.72 Other clinical findings associated with hyperthyroidism include weight loss, polyphagia, increased activity, and enlargement of the thyroid gland.

The definition of TS in human medicine includes presence of GI or hepatic signs. In 1 human study, presence of nausea, vomiting, or diarrhea was not frequent in patients with non-TS thyrotoxicosis. The significance of this finding is unclear in veterinary medicine, because many cats with hyperthyroidism have GI signs as a presenting complaint.73

**Diagnosis**

Presumptive diagnosis of TS is made by identifying compatible clinical signs in an animal with known or suspected hyperthyroidism. Some presenting with TS may already be undergoing therapy for hyperthyroidism, so the index of suspicion should be heightened for those patients. Hyperthyroidism can be confirmed by identifying an increased total T₄, increased free T₄ with a high normal total T₄, or failure to suppress with triiodothyronine (T₃) suppression test. Technetium scan of the thyroid is also an accurate way of diagnosing hyperthyroidism and identifying ectopic tissue.74,75

To rule out other causes of crisis and identify any underlying catalysts for TS, a complete patient evaluation is warranted, including a CBC, chemistry, urinalysis, urine culture, retroviral testing, and thoracic and abdominal imaging. Clinicopathologic abnormalities are as expected for any case of hyperthyroidism, and may include mild erythrocytosis, macrocytosis, a stress leukogram, increased liver enzyme activities, hypokalemia, and mild hyperglycemia. Thoracic radiographs may reveal cardiomegaly or biatrial enlargement, with or without evidence of CHF, pulmonary edema, or pleural effusion. Echocardiogram may show left ventricular and interventricular hypertrophy and atrial enlargement.76,77

**Emergency Management of Thyrotoxicosis/TS**

Treatment of thyrotoxic crisis or TS must address the systemic manifestations of thyrotoxicosis as well as reduce the hormone excess. In the midst of a thyroid crisis, eliminating clinical signs is accomplished most rapidly by reducing tachycardia, tachyarrhythmias, and hypertension. Arrhythmias in TS can typically be treated via ß-blockade using esmolol, atenolol, or propranolol. Esmolol is a short-acting selective ß₁-blocker that must be administered as CRI. Atenolol is also a selective ß₁-blocker, but only available orally. Propranolol is a nonselective ß-blocker that can be given both injectably and orally. ß-Blockers should be used with caution in patients with CHF, because ß-blockade can reduce cardiac contractility and exacerbate CHF. A hypertensive crisis may require a rapidly acting vasodilatory drug such as nitroprusside or hydralazine. Both can be given injectably; nitroprusside is given as a CRI and is titrated to effect. Amlodipine takes several days to reach maximal effect, so it is effective for treating hypertension only in the noncrisis state. See Table 5 for drug doses.

Reducing thyroid levels is crucial for effective treatment of TS. Methimazole prevents synthesis of new thyroid hormone and can be given orally, rectally, and transdermally.78,79 Plasmapheresis or plasma exchange could also be used to reduce blood thyroid hormone levels, but these are not readily available.80 Because large quantities of hormone can be stored in the thyroid, additional treatment is aimed at reducing hormone release from the thyroid gland. Iodine, in the form of sodium or potassium iodide or potassium iodate, reduces thyroid hormone concentrations by inhibiting oxidation of iodide in the thyroid gland, formation of thyroid hormone within follicles, and secretion of hormone from the gland.81,82 These drugs must be given at least 1 hour after
methimazole to prevent increased iodine uptake and subsequent hormone production by the thyroid. However, when given in conjunction with antithyroid medications, the thyroid levels decrease dramatically. Iopanoic acid (50–100 mg, twice a day, by mouth) decreases conversion of T4 to T3 and decreased mean serum T3 concentrations by more than 50% in 1 study. Ipodate (sodium or calcium) also decreases conversion of T4 to T3 and may also block T3 receptors and effects of thyroid-stimulating hormone (TSH). It is not available commercially, but may be available via compounding pharmacies. See Table 5 for dosing.

Symptomatic and supportive care is the final phase of treatment of TS and may continue after the crisis is past. Concurrent cardiac failure may require oxygen therapy, furosemide diuresis, and venodilation with nitroglycerin paste. Additional cardiac medications such as pimobendan, an angiotensin-converting enzyme inhibitor (eg, benazepril, enalapril) and a calcium channel blocker (eg, diltiazem) may also be indicated based on echocardiographic evaluation. β-Blockade is continued at least until the hyperthyroidism is definitively treated. Cats that remain hypertensive after the TS crisis should be treated with an antihypertensive drug such as amlodipine, because β-blockade alone is not sufficient to treat ongoing hypertension.

Miscellaneous therapies that may be indicated for TS include antithrombotic therapy and electrolyte or dextrose supplementation. Anticoagulants, such as heparin or warfarin, or antiplatelet drugs, such as aspirin or clopidogrel, may be indicated for cats with evidence of thrombosis or spontaneous contrast in the atria on echocardiogram. Potassium supplementation (IV or by mouth) may be required to treat hypokalemia. IV fluids containing dextrose may help replenish hepatic glycogen levels. Any concurrent disease processes should also be addressed, because they may have contributed to development of TS.

Postcrisis Management of Hyperthyroidism

Once the thyrotoxic crisis has passed, hyperthyroidism must be managed long-term. Chronic methimazole therapy, radioactive iodine (I131), surgical thyroidectomy, and dietary management are all possible strategies. There are no data in veterinary medicine regarding which of these may be the best or least ideal therapy in regards to preventing recurrence of TS. In human medicine, definitive therapy with radioactive iodine or surgery is preferred. Hypertension may also require chronic management. Thyrotoxic cardiac changes are largely reversible with appropriate treatment of the hyperthyroidism, and patients with historical thyrotoxicity-induced CHF may be amenable to withdrawal of cardiac medications.

Prognosis

Prognosis for a true TS is unknown for veterinary patients. Mortality in humans is reportedly 10% to 75%. Early recognition and appropriate, timely interventions are likely imperative for a positive outcome.

HYPOTHYROIDISM: MYXEDEMA COMA

As reviewed earlier, thyroid hormone plays pivotal roles in the body. It governs the metabolic rate and is essential to normal function of most tissues, including the neurologic and cardiovascular systems. Severe hypothyroidism rarely manifests as myxedema coma, a life-threatening condition marked by altered mental status, hypothermia, and mucinous skin edema. Hypotension, hypoventilation, and other signs of hypothyroidism may also be present (Box 2). As with many endocrine crises, myxedema coma is often precipitated by another condition, such as an infection,
Box 2
Clinical signs associated with hypothyroidism

*Reduced Metabolism*
- Weight gain
- Weakness, lethargy
- Exercise intolerance
- Cold intolerance

*Neurological/Muscular*
- Peripheral neuropathy
- Paraparesis/tetraparesis
- Lameness (unilateral, forelimb)
- Variable cranial nerve dysfunction
- Central vestibular signs
- Megaesophagus
- Laryngeal paralysis
- Cognitive dysfunction

*Ophthalmic*
- Corneal lipid
- Corneal ulceration
- Lipid aqueous
- Lipemia retinalis
- Retinal detachment

*Cardiovascular*
- Sinus bradycardia
- Reduced cardiac contractility
- Reduced electrocardiograph voltages, inverted T waves
- Atherosclerosis
- Vascular events

*Dermatologic*
- Bilateral, symmetric alopecia
- Hyperpigmentation
- Scaly skin
- Seborrhea sicca
- Seborrhea oleosa
- Pyoderma

*Reproductive (Possibly)*
- Unpredictable cycling in females
- Spontaneous abortions
- Weak or stillborn pups
- Low libido
- Testicular atrophy
- Low sperm count

\[a\] The most common clinical findings.
nonthyroidal illness, certain drugs, diet, or even cold weather, that overwhelms the normal compensatory mechanisms of the body.68

The term myxedema coma is a misnomer, because coma is rare. Both central and peripheral neurologic deficits may be seen in hypothyroidism, although peripheral deficits are more common. CNS deficits can occur in hypothyroidism as a result of myxedema coma, atherosclerosis, hyperlipidemia, or presence of a pituitary tumor causing secondary hypothyroidism. The most common central neurologic manifestations include weakness and dull mentation or stupor caused by cerebral edema. Concurrent dilutional hyponatremia may also contribute to neurologic signs. Profound weakness and cerebral edema can also contribute to hypoventilation and hypoxemia.89

Hypothermia occurs because the metabolic rate decreases in the absence of thyroid hormone, and this subsequently reduces the amount of heat generated as a by-product of cellular respiration. Cerebral edema or presence of a pituitary tumor can interfere with the hypothalamic thermoregulatory set point, and shivering is also decreased as a result of lack of thyroid stimulation of muscular activity.69 Bradycardia and hypotension may also occur, because thyroid hormone normally indirectly stimulates cardiac rate and contractility by increasing the number of β-adrenergic receptors and sensitizing the cardiovascular system to catecholamines.

Myxedema, also known as cutaneous mucinosis, is a nonpitting edema of the skin that occurs in severe hypothyroidism when glycosaminoglycans and water accumulate within the interstitium of the dermis. The myxedema tends to be most prominent over the head and face and can be a clue to the presence of this hypothyroid crisis.

Diagnosis

Presumptive diagnosis of myxedema coma is via history, physical examination and supportive findings on diagnostic evaluation. Given the severity of clinical signs, a complete diagnostic workup, including CBC, chemistry, urinalysis, urine culture, and thoracic and abdominal imaging, is indicated. General clinicopathologic abnormalities include mild nonregenerative anemia (because T4 stimulates erythropoiesis), hyperlipidemia, hypercholesterolemia (because T4 governs cholesterol synthesis and degradation), hypoglycemia, a dilutional hyponatremia, and increased alkaline phosphatase levels.85,87,90

Thyroid testing

Confirmation of hypothyroidism requires specific thyroid testing. Dogs with myxedema coma should have thyroid function tests that are consistent with hypothyroidism, including a low free T4 by equilibrium dialysis, low total T4, and an increased TSH.87,90 Secondary hypothyroidism (TSH deficiency) is rare, and tertiary hypothyroidism (thyrotropin-releasing hormone deficiency) has not been documented in dogs.

Emergency Management of Myxedema Coma

Successful treatment of a hypothyroid crisis must include stabilization of the cardiovascular and respiratory systems and supplementation of thyroid hormone. The first step is to ensure a patent airway and adequate ventilation based on blood gas analysis. Oxygen should be supplemented if the animal is hypoxic; the patient should be intubated and ventilated if hypercapnic.85 Hypotension should be managed with judicious fluid therapy, because cardiac dysfunction and retention of free water may predispose the patient to fluid overload. An initial bolus of 20 to 30 mL/kg of replacement crystalloids (such as LRS or Normosol-R) is often indicated, with repeat boluses and development of a postresuscitation fluid therapy plan based on response to therapy.
Slow rewarming of the patient is also indicated; rapid rewarming causes vasodilation, which can exacerbate hypotension.

True myxedema coma is life-threatening and requires empirical thyroid hormone supplementation before the return of thyroid function tests. IV levothyroxine (5 μg/kg [0.005 mg/kg] every 12 hours) is recommended. To prevent overtaxing a weak heart, a lower dose may be indicated if significant underlying heart disease or heart failure is present. Once the patient is stable and able to swallow oral medications, oral levothyroxine therapy should be started (see Table 5). If injectable levothyroxine is unavailable from a local pharmacy or hospital, enteral supplementation can be attempted via a nasoesophageal or orogastric tube in those unable to swallow.

**Postcrisis Management of Hypothyroidism**

After stabilization, lifelong supplementation with oral T₄ is required. Therapy is titrated using routine measurement of T₄, initially monthly until clinical signs resolve and the T₄ is within or just above reference range 4 to 6 hours after dosing, then 1 to 2 times yearly in an otherwise asymptomatic and clinically well patient.⁹¹

**Prognosis**

Prognosis for myxedema coma hinges on timely recognition and institution of appropriate therapy. Successful treatment has been reported in dogs with severe hypothyroidism.⁸⁷,⁹⁰ In humans, mortality has historically been up to 70% but has improved to 20% to 25% with intensive care and hormonal therapy.⁶⁸

**SUMMARY**

Endocrine emergencies present with a wide spectrum of nonspecific signs and symptoms.

Familiarity with the clinical presentations of these endocrine crises facilitates early recognition, appropriate treatment, and improved outcomes for patients.

**REFERENCES**

**DIABETIC EMERGENCIES**


HYPOGLYCEMIA: EXOGENOUS AND ENDOGENOUS INSULIN OVERDOSE (INSULINOMA)


HYPOADRENOCORTICISM


**PHEOCHROMOCYTOMA**


THYROTOXICOSIS/THYROID STORM


**MYXEDEMA COMA**