Soloviova Liudmyla/shutterstock.com

Abstract

Diabetic ketoacidosis (DKA) is one of the most common endocrine emergencies in cats and dogs and can be fatal without medical intervention. Extreme hyperglycemia leading to hypovolemic shock and severe electrolyte imbalances in conjunction with ketone formation leading to acidemia characterize this complicated disease process. This article summarizes the pathophysiology of DKA and how to stabilize and initiate treatment in patients presenting with DKA.

CONTINUING EDUCATION

INTERNAL MEDICINE

Diabetic Ketoacidosis: Causes, Recognition, and Treatment

***Ranelle Thomas**, BS, RVT, VTS (ECC)*
Veterinary Emergency Group, San Diego, California

To understand how diabetic ketoacidosis (DKA) develops, it is important to know how the body normally uses glucose for energy and its compensatory mechanisms if energy needs are not being met.

NORMAL GLUCOSE METABOLISM

In a healthy patient, insulin and glucagon work together to maintain a stable glucose level that allows cells to perform functions essential for life (**BOX 1**).[1] When blood glucose levels are high, the β-cells of the islets of Langerhans in the pancreas secrete insulin,[2] which binds to insulin receptors on cell membranes. This binding allows glucose to enter the cell, where it is converted into adenosine triphosphate (ATP) through cellular respiration. ATP is the main energy source for cells. Once cells' energy needs are met, insulin stimulates conversion

Take-Home Points

- Insulin and glucagon perform opposite functions to maintain a stable glucose level that fulfills cellular energy needs.
- Diabetes mellitus is caused by a lack of insulin production or by insulin resistance.
- Concurrent diseases stimulate the release of diabetogenic hormones, which increase metabolic energy requirements.
- Acidic ketone bodies are formed when triglycerides cannot be metabolized normally, leading to acidemia.
- Fluid therapy to correct hypovolemia caused by osmotic diuresis is the most important first step in stabilization of patients with diabetic ketoacidosis (DKA).
- The hallmarks of DKA are hyperglycemia, ketonemia, and acidemia.
- Insulin therapy should be initiated within 6 hours of presentation.
- Blood glucose and electrolytes should be closely monitored throughout hospitalization, and supplementation should be adjusted accordingly.
- Concurrent diseases will largely determine other necessary treatments.
- Owners need to be informed of the financial and emotional commitment of not only the hospitalization but also a likely lifelong disease.

of excess glucose into glycogen that can be stored in the liver. Insulin also causes amino acids to be stored as protein and fatty acids to be stored in adipose tissue.[3]

If cells' energy needs are not being met (e.g., during fasting), the α-cells of the islets of Langerhans secrete glucagon. Glucagon is insulin's opposite: It stimulates glycogenolysis (breakdown of glycogen into glucose), proteolysis (breakdown of protein into amino acids), and lipolysis (breakdown of adipose tissue into fatty acids). The body then uses the released glucose and other components to maintain consistent energy production.

Not all glucose can be immediately transported into cells or converted into glycogen. Some remains in the bloodstream and travels to the kidneys, where, in a normal, healthy patient, the proximal convoluted tubule of the nephron reabsorbs it so it can reenter circulation.[2] However, there is a limit to how much glucose the tubules can reabsorb; this is referred to as the renal threshold and is normally 180 to 220 mg/dL.[4] As long as blood glucose is below this threshold, glucose should never be excreted into the urine. It is all used for energy or stored as glycogen.

PATHOPHYSIOLOGY OF DIABETES MELLITUS

When there is a deficiency in insulin, diabetes mellitus develops. Without adequate insulin, glucose in the bloodstream cannot enter cells at sufficient levels to meet energy needs, leading to cell starvation. In response, glucagon is secreted to increase the breakdown of glycogen, protein, and fat. The result is a huge increase in glucose, but still little to none of it can enter the cells. Blood glucose rises to surpass the renal threshold and excess glucose is secreted into the urine.[1] Due to glucose's high osmolality, more water is pulled into the urine, leading to polyuria. The resulting free water loss, along with the lack of cellular energy, stimulates the hunger and thirst control centers of the hypothalamus, causing polydipsia and polyphagia.[2] However, despite the patient eating more and appearing hungry more often, weight loss occurs as muscle and fat continue to be broken down in the ongoing absence of insulin. Polyuria, polydipsia, polyphagia, and weight loss are the typical presenting concerns of clients with diabetic pets. Dogs may also experience cataract formation caused by accumulation of fluid in the lens and subsequent lens fiber rupture.[4]

Why is there suddenly an inadequate amount of insulin? In dogs and cats, there are 2 general reasons: insulin deficiency and insulin resistance (**BOX 2**). Insulin deficiency is the result of loss of functioning β-cells,[4] leading to a decrease in the overall amount of insulin in the body. Insulin resistance occurs when cells have reduced sensitivity to insulin and therefore do not use it in appropriate amounts. In addition, β-cells fail to compensate for this reduced sensitivity and do not

BOX 1

Functions of Insulin and Glucagon

Insulin
- Glucose utilization
- Glycogen formation
- Protein and fat storage

Glucagon
- Glycogenolysis
- Proteolysis
- Lipolysis

BOX 2

Causes of Diabetes Mellitus in Dogs and Cats[4,5]

Insulin deficiency
- Congenital hypoplasia
- Immune-mediated destruction of β-cells
- Pancreatitis
- Prolonged insulin resistance

Insulin resistance
- Pregnancy/diestrus
- Hyperadrenocorticism (Cushing's disease)
- Renal insufficiency
- Obesity
- Physical inactivity
- Chronic inflammation
- Administration of glucocorticoids or progestins

BOX 3

Common Concurrent Diseases in Patients With Diabetic Ketoacidosis[3]

Dogs

- Pancreatitis
- Bacterial urinary tract infection
- Hyperadrenocorticism

Cats

- Hepatic lipidosis
- Chronic renal failure
- Pancreatitis
- Bacterial or viral infections
- Neoplasia

increase insulin secretion; this failure is not fully understood.[5] The clinical difference between insulin deficiency and insulin resistance may not be entirely important; however, it is estimated that 80% to 90% of cats with diabetes mellitus are insulin resistant, which is why cats can go into remission (i.e., there is no loss of functioning β-cells).[5] β-Cell loss cannot be reversed, and patients with β-cell loss cannot go into remission.

PROGRESSION TO DIABETIC KETOACIDOSIS

Patients can compensate for undiagnosed diabetes mellitus for weeks to months without severe consequences, as long as there is some circulating insulin.[6] However, if another disease develops (**BOX 3**), metabolic homeostasis becomes more difficult to achieve and compensatory mechanisms are quickly overwhelmed and begin to fail. A retrospective study found that of 127 dogs diagnosed with DKA, 70% had concurrent diseases, with 20% having a urinary tract infection, 15% having hyperadrenocorticism, and 6% having pneumonia.[7]

Stress, such as concurrent illness, stimulates the release of catecholamines (epinephrine and norepinephrine), cortisol, growth hormone, and glucagon.[6,8] Referred to as diabetogenic, or glucose counter-regulatory, hormones, these hormones increase blood glucose concentration through glycogenolysis, gluconeogenesis,

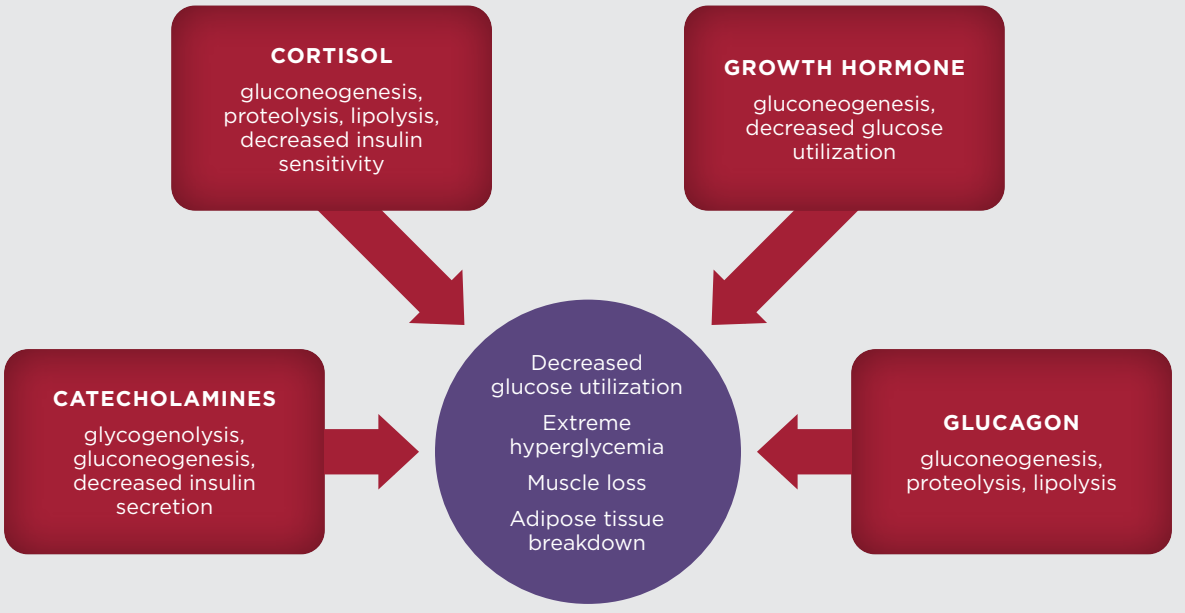

FIGURE 1. Diabetogenic hormones and their effects.[9] Extreme stress, including illness, causes the adrenal medulla to secrete catecholamines. Cortisol, a glucocorticoid that suppresses immune response, is secreted by the cortex of the adrenal gland during times of fasting. Growth hormone is secreted by the anterior lobe of the pituitary gland in response to stress. Glucagon is secreted by the pancreas in response to inadequate cellular energy production. In diabetic patients, the combined effect of these hormones exacerbates existing hyperglycemia and muscle and fat breakdown.

lipolysis, and/or proteolysis (**FIGURE 1**). In a normal patient, these hormones help support the body during a stressful event by increasing the amount of glucose available to be converted into energy. In diabetic patients, the resulting level of hyperglycemia—added to the demands of an activated immune system and the effects of ongoing total body cell starvation, water loss, and breakdown of muscle and fat—leads to increasingly detrimental attempts to compensate.

Ketone Formation and Acidemia

Lipolysis increases the level of free fatty acids, which are converted by the liver into acetyl coenzyme A (acetyl-CoA). Normally, acetyl-CoA enters the citric acid (Kreb's) cycle to form ATP, but in diabetic patients, due to depletion of other enzymes during gluconeogenesis, it is instead converted into β-hydroxybutyrate, which is further broken down into acetoacetate and acetone.[2,8] β-Hydroxybutyrate, acetoacetate, and acetone are all ketones, which are acidic.

In DKA, the rising ketone concentration eventually leads to acidemia (lowering of pH in the blood).[8] As ketone levels increase, the pH continues to decrease. Because cells only function within a very narrow pH range (7.35 to 7.45), the increasing acidemia can cause multiple metabolic disruptions.[6]

Hypovolemic Shock and Electrolyte Imbalances

Excretion of ketones into the urine further exacerbates osmotic diuresis. At this point, water loss dehydrates the patient to the point of hypovolemia. Hypovolemia leads to low cardiac output because stroke volume is decreased, and hypotension occurs, compromising oxygen delivery to the tissues and resulting in poor perfusion to all vital organs. The renin-angiotensin-aldosterone system is activated in an attempt to increase cardiac output by decreasing water loss and increasing systemic vascular resistence. However, the degree of continued diuresis in DKA patients overwhelms this compensatory system, resulting in hypovolemic shock.

Osmotic diuresis also causes severe electrolyte disturbances resulting from excess excretion of sodium, potassium, magnesium, and phosphorus by the kidneys into the urine. The body compensates by shifting intracellular stores into the extracellular fluid (plasma), but a total body deficit of each electrolyte remains. Sodium is particularly affected, as most sodium is stored in the extracellular fluid and has already been depleted due to water loss; therefore, hyponatremia cannot be compensated for in this way.

PRESENTATION OF DIABETIC KETOACIDOSIS

As in normal diabetic patients, presenting complaints for patients with DKA usually include polyuria, polydipsia, polyphagia, and weight loss. Other clinical signs depend on concurrent disease(s) and may include vomiting and/or regurgitation, diarrhea, anorexia, abnormal breathing or dyspnea, stranguria, or outward signs of infection (e.g., skin, upper respiratory tract).

On physical examination, the patient may be tachycardic or bradycardic; have weak pulses, a low body temperature due to hypotension, a fever due to infection, a dull mentation, or abdominal distention secondary to concurrent diseases (e.g., hepatomegaly, pancreatitis)[8]; display Kussmaul respiration[8]; or be dyspneic, in cases of pneumonia.

Kussmaul respiration is characterized by rapid, deep breaths and is an attempt to blow off extra carbon dioxide, which is acidic, to compensate for acidemia. Mucous membranes may be pale due to peripheral vasoconstriction from hypotension or appear icteric from hepatopathy.

Most patients appear cachexic, have a poor body condition score, and have sunken eyes from muscle and fat breakdown and dehydration. Some may have the smell of acetone detectable on their breath.

STABILIZATION OF DIABETIC KETOACIDOSIS

Even before diagnosis, any patient presenting with severe lethargy in addition to many of the above clinical signs should have an intravenous catheter immediately placed and flow-by oxygen administered, if applicable.

After the degree of dehydration is assessed and cardiopulmonary auscultation is performed, fluid resuscitation is critical. If the degree of hypotension warrants it, sequential, small-volume boluses (5 to 10 mL/kg for cats, 10 to 20 mL/kg for dogs) should be given until the patient is normotensive; however, fluid therapy should continue. Heat support may be indicated for hypothermic patients.

DIAGNOSTIC TESTING

To diagnose DKA, hyperglycemia, ketonemia or ketonuria, and acidemia must be present. Measuring ketonemia has proven to be more accurate and effective in diagnosing DKA than is assessing ketonuria.[10] Obtaining a small blood sample may also be easier than collecting urine from a severely dehydrated patient.

Blood Glucose, Ketones, and pH Measurement

To measure blood glucose and ketones, cage-side glucometers and ketometers provide fairly rapid results, and each requires only a drop of blood. In patients with DKA, the blood glucose often exceeds 500 mg/dL; in many cases, it is too high to read. For the commonly used AlphaTRAK glucometer (Zoetis; **zoetispetcare.com**), this means the blood glucose is over 750 mg/dL.

Cutoff values for DKA on ketometers seem to vary slightly. One study found that a value > 2.4 mmol/L in cats was sufficient to diagnose DKA,[11] while another concluded that > 3.8 mmol/L was the best cutoff value for monitoring ketosis and ketoacidosis in dogs.[12] If a ketometer is not available, urine strips can be used to measure ketonuria; however, they are less sensitive and accurate in showing the degree of ketosis because they do not detect β-hydroxybutyrate.

Blood gas must be measured to obtain the pH status of the patient. Metabolic acidosis is a hallmark of DKA.

Complete Blood Count, Serum Biochemistry, and Electrolyte Testing

A complete blood count (CBC) and full serum biochemistry and electrolyte profile should be performed as soon as possible. The CBC may reveal hemoconcentration from dehydration; however, anemia is present in approximately 20% of patients.[8] A blood smear may show Heinz body formation in cats, which has been correlated with the presence of β-hydroxybutyrate.[3] Leukocytosis, if present, indicates inflammation or infection.

Potassium, magnesium, and phosphorus levels may initially be normal or low; however, sodium will always be low due to free water loss. Increased alanine aminotransferase, alkaline phosphatase, and total bilirubin levels may be seen due to diabetic hepatopathy, decreased hepatic perfusion, hepatic lipidosis, pancreatitis, or any combination of these.[8]

Diabetic hepatopathy and hepatic lipidosis occur due to the greatly increased mobilization of free fatty acids to the liver to be metabolized into acetyl-CoA. Decreased hepatic perfusion occurs due to hypovolemia.

Elevated kidney values (blood urea nitrogen and creatinine) may also be seen due to hypovolemia causing decreased renal perfusion (prerenal azotemia). Kidney values may be increased due to acute or chronic concurrent kidney disease. Hyperlipidemia may be seen in serum or plasma because of the increased concentration of free fatty acids in the blood and because insulin deficiency prevents activation of lipoprotein lipase, which would decrease the number of circulating triglycerides.[8]

Urine Testing

A sterile urine sample should be obtained prior to any antibiotic therapy and submitted for culture and sensitivity testing. The urine will appear very dilute, but the specific gravity may be higher than expected (1.025 to 1.035) due to the amount of glucose[1] and ketones present. A urine strip will confirm glucosuria and show ketonuria.

Imaging

Thoracic and/or abdominal radiographs should be obtained to rule out neoplasia and metastatic disease, which may alter prognosis and the owner's desire to proceed with treatment. Pneumonia may also be confirmed. Once the patient is stable, a full abdominal ultrasound examination should be considered to assess for intra-abdominal diseases such as pancreatitis, chronic kidney disease, hepatic lipidosis, and neoplasia.

INSULIN THERAPY

After fluid therapy, the most important intervention in treating a patient with DKA is starting insulin treatment. Fluid therapy helps correct hypovolemia, rehydrate the patient, and dilute the concentrations of glucose and diabetogenic hormones. Insulin is necessary to metabolize ketone bodies, thereby correcting acidemia.[8]

A recent retrospective study found that starting insulin within 6 hours of presentation was associated with more rapid resolution of ketonemia and acidemia.[13] Several methods of providing insulin have been

successfully used to treat DKA, but a consensus on which is superior has yet to be established by the veterinary community; therefore, the method chosen will be the veterinarian's preference.

Constant-Rate Infusion of Regular Insulin

Constant-rate infusion (CRI) is currently the most common method of insulin administration in patients with DKA. The benefits of using an insulin CRI are less discomfort to the patient (compared with intramuscular injections) and ease of adjustment. CRI offers the most control in stabilizing blood glucose. However, the blood glucose should ideally be monitored hourly, and adjustments might be needed every hour, which can be tedious and expensive. In addition, if the CRI is running at a high rate and there is a delay in checking blood glucose, iatrogenic hypoglycemia can result.

To set up an insulin CRI:

- Add 2.2 U/kg (dogs) or 1.1 U/kg (cats) of regular insulin into a 250-mL bag of 0.9% saline.
- "Bleed" the drip set and all connected extension lines with 50 mL of the solution because insulin binds to plastic.

The CRI is run in conjunction with crystalloid fluids, and the rate of crystalloid fluids should be adjusted depending on the insulin CRI rate, which is determined by the patient's blood glucose (**TABLE 1**). For example, if a patient needs to receive 150 mL/h of fluid and the patient's blood glucose is 570 mg/dL, the crystalloid rate should be 140 mL/h because the insulin CRI rate will be 10 mL/h. This adjustment is to avoid fluid overload, especially in cats and smaller dogs, which require much lower fluid rates.

Intermittent Injections of Glargine

One study effectively treated 15 cats with DKA by using a combination of intramuscular and subcutaneous glargine injections.[14] In this study, 1 to 2 units of glargine were given intramuscularly up to every 2 hours in addition to 1 to 3 units of glargine given subcutaneously every 12 hours. There has been some apprehension in recommending this protocol because 2 of the 15 cats in the study required blood transfusions due to hypophosphatemia, but it is unknown if this was due to the protocol or to the disease process itself.[1] Additional research using this protocol is required to better evaluate its efficacy and safety.

Intermittent Injections of Regular Insulin and Glargine

Another study investigating cats with DKA found that combining intramuscular regular insulin with subcutaneous glargine resulted in more rapid resolution of ketonemia than using a regular insulin CRI.[15] Regular insulin was administered at 1 unit up to every 6 hours and glargine was given at 0.25 U/kg every 12 hours. Additional research is needed, especially in dogs, to confirm this protocol's superiority to using only regular insulin CRI.

MONITORING AND ELECTROLYTE SUPPLEMENTATION

Regardless of the type of insulin protocol used, the blood glucose will need to be frequently checked. Placing a central venous catheter or a sampling catheter not only allows veterinary nurses to obtain samples easily but also helps decrease patient discomfort by limiting the number of venipunctures performed. Ideally, blood glucose is checked every hour, especially if an insulin CRI is being used, so that the insulin dose can be adjusted accordingly.

TABLE 1 Insulin CRI Rate and Dextrose Supplementation Based on Patient Blood Glucose[8]

BLOOD GLUCOSE (mg/dL)	CRYSTALLOID DEXTROSE CONCENTRATION (%)[a]	INSULIN RATE (mL/h)
>250	0	10
200–250	2.5	7
150–200	2.5	5
100–150	5	5
<100	5	0

[a]*Dextrose is added to the crystalloids to maintain a stable blood glucose level and mimic homeostasis between glucose and insulin.*
CRI = constant-rate infusion

BOX 4

Calculating Potassium Dose Safety

To calculate whether a potassium dose will exceed 0.5 mEq/kg/h, divide the dose by 1000 mL, then multiply by the fluid rate and divide by the patient's weight in kilograms.

Example 1: A 5-kg patient is receiving fluids at 25 mL/h. The clinician orders 60 mEq/L of potassium. Is this dose safe to add to the current fluid therapy?

(60 mEq ÷ 1000 mL) × (25 mL/h) ÷ (5 kg) = 0.3 mEq/kg/h

This dose is less than 0.5 mEq/kg/h and is safe to give.

Example 2: An 8-kg patient is receiving fluids at 85 mL/h. The clinician orders 50 mEq/L of potassium. Is this dose safe to add to the current fluid therapy?

(50 mEq ÷ 1000 mL) × (85 mL/h) ÷ (8 kg) = 0.53 mEq/kg/h

This dose is more than 0.5 mEq/kg/h and is not safe to give.

Fluid therapy alone lowers blood glucose and causes some electrolytes (e.g., potassium, magnesium, phosphorus) to shift back into the intracellular space, revealing the true total body electrolyte deficit. Insulin also causes potassium and phosphorus to shift intracellularly; therefore, insulin therapy further exacerbates hypokalemia and hypophosphatemia.[16] Hypokalemia can cause generalized skeletal muscle weakness, potentially leading to impaired ventilation; hypophosphatemia can cause muscle weakness, altered mental status, and hemolysis of red blood cells.[16] Hypomagnesemia can cause twitching and arrhythmias. Electrolyte supplementation may therefore be needed.

Scott's sliding scale (**TABLE 2**) can be used to calculate an appropriate amount of potassium supplementation, but the potassium administration rate should not exceed 0.5 mEq/kg/h (**BOX 4**). Doses of potassium supplementation that exceed this rate can lead to iatrogenic hyperkalemia, which can cause bradycardia that can progress to death. Recommended dosing for phosphorus supplementation is variable, but most sources indicate to supplement phosphorus with potassium phosphate and base the dose on the patient's potassium level.[16] Magnesium can be supplemented at a dose of 0.7 to 1 mEq/kg/day.[16]

TREATING CONCURRENT DISEASES

Each patient with DKA is treated differently depending on its concurrent disease(s). Although details of individual treatment protocols are beyond the scope of this article, they may include antibiotics, antinausea medications and prokinetics, hepatic support medications, nasogastric tube placement, oxygen therapy, and nebulization treatment. Pain medications and/or anxiolytics should be considered and advocated for, as pain and anxiety induce a stress response, increasing the release of diabetogenic hormones.

PROGNOSIS AND CLIENT EDUCATION

The goals of treatment of patients with DKA are to correct ketonemia and acidemia, restore and maintain fluid balance, and treat concurrent diseases.[8] One study found that the degree of acidemia was associated with survival—the worse the acidemia, the poorer the outcome.[7]

Once these goals are achieved and the patient is eating, long-acting insulin can be administered. Ideally the blood glucose should be monitored for the next 12 to 24 hours to ensure correct dosage before discharge. Up

TABLE 2 Scott's Sliding Scale for Potassium Supplementation[16]

MEASURED SERUM K^+ CONCENTRATION (mEq/L)	KCL (mEq) TO ADD TO 1 L OF FLUIDS	MAXIMUM FLUID RATE (mL/kg/h)
<2	80	6
2.1–2.5	60	8
2.6–3	40	12
3.1–3.5	30	18
3.6–5	0–20	25

K^+ = potassium, KCL = potassium chloride

to 70% of patients diagnosed with DKA survive to discharge.[7] However, upon diagnosis of DKA, the patient's owner needs to be informed about the financial undertaking of an extended hospitalization and that certain concurrent diseases, such as pancreatitis, can prolong the time it takes to reach recovery[7] and increase cost. DKA is not a disease that can be treated halfway, and owners must understand the financial commitment before initiating treatment. Diabetes is also a new diagnosis for many patients with DKA[3]; therefore, client education about diabetes mellitus and compliance with at-home treatment are paramount for the health of the patient once discharged. Upon discharge, owners should also be advised of warning signs of general illness, as all diabetic patients are at risk of going into DKA with any additional stress. Early recognition of sickness is therefore crucial to limiting future hospitalization.

SUMMARY

DKA is a medical emergency characterized by hyperglycemia, ketonemia, and acidemia. Concurrent illnesses make treating each patient unique, but fluid resuscitation and insulin therapy are essential to resolving hypovolemic shock and life-threatening acidemia in all patients with DKA. These patients require frequent reevaluation of hydration status and vital parameters and diligent monitoring of electrolytes and blood glucose. Because DKA is one of the most common endocrine emergencies in veterinary medicine, it is important for veterinary nurses to understand how and why this condition occurs to be better able to give excellent care to these critical patients. TVN

Ranelle Thomas

Ranelle began her veterinary career as a volunteer at an animal shelter. After graduating from UC Santa Cruz in 2012, she entered the veterinary technology program at Foothill College in California. She completed an internship with Adobe Animal Hospital and then became an RVT in its intensive care unit. She subsequently obtained her VTS credential in emergency and critical care in 2019. In 2021, she moved to San Diego to work for Veterinary Emergency Group. She enjoys teaching in a dynamic emergency room and continuing to learn and grow in this ever-evolving field.

References

1. Fults M. Canine diabetes mellitus: it's about the sugar. *Todays Vet Tech*. 2016;1(1):71-78.
2. Endocrine system. In: Aspinall V, Cappello M, eds. *Introduction to Animal and Veterinary Anatomy and Physiology*. 4th ed. CAB International; 2020:73-78.
3. Hess RS. Diabetic ketoacidosis. In: Silverstein DC, Hopper K, eds. *Small Animal Critical Care Medicine*. 2nd ed. WB Saunders, 2015:343-346.
4. Fracassi F. Canine diabetes mellitus. In: Ettinger SJ, Feldman EC, Côté E, eds. *Textbook of Veterinary Internal Medicine*. 8th ed. Elsevier; 2017:1767-1781.
5. Rand J, Gottlieb SA. Feline diabetes mellitus. In: Ettinger SJ, Feldman EC, Côté E, eds. *Textbook of Veterinary Internal Medicine*. 8th ed. Elsevier; 2017:1781-1795.
6. Rudloff E. Diabetic ketoacidosis in the cat: recognition and essential treatment. *J Feline Med Surg*. 2017;19(11):1167-1174. doi:10.1177/1098612X17735762
7. Hume DZ, Drobutz KJ, Hess RS. Outcome of dogs with diabetic ketoacidosis: 127 dogs (1993-2003). *J Vet Intern Med*. 2006;20(3):547-555. doi:10.1892/0891-6640(2006)20[547:oodwdk]2.0.co;2
8. Thorp AJ. Endocrine and metabolic emergencies. In: Norkus CL, ed. *Veterinary Technician's Manual for Small Animal Emergency and Critical Care*. 2nd ed. John Wiley & Sons, Inc; 2019:175-190.
9. Endocrine physiology. In: Costanzo LS, ed. *Costanzo Physiology*. 7th ed. Elsevier; 2022:399-463.
10. Di Tommaso M, Aste G, Rocconi F, Guglielmini C, Boari A. Evaluation of portable meter to measure ketonemia and comparison with ketonuria for the diagnosis of canine diabetic ketoacidosis. *J Vet Intern Med*. 2009;23(3):466-471. doi:10.1111/j.1939-1676.2009.0302.x
11. Weingart C, Lotz F, Kohn B. Measurement of ß-hydroxybutyrate in cats with nonketotic diabetes mellitus, diabetic ketosis, and diabetic ketoacidosis. *J Vet Diagn Invest*. 2012;24(2):295-300. doi:10.1177/1040638711428332
12. Duarte R, Simoes DMN, Franchini ML, Marquezi ML, Ikesaki JH, Kogika MM. Accuracy of serum ß-hydroxybutyrate measurements for the diagnosis of diabetic ketoacidosis in 116 dogs. *J Vet Intern Med*. 2008;16(4):411-417. https://doi.org/10.1111/j.1939-1676.2002.tb01258.x
13. DiFazio J, Fletcher DJ. Retrospective comparison of early-versus-late-insulin therapy regarding effect on time to resolution of diabetic ketosis and ketoacidosis in dogs and cats: 60 cases (2003-2013). *J Vet Emerg Crit Care (San Antonio)*. 2016;26(1):108-115. doi:10.1111/vec.12415
14. Marshall RD, Rand JS, Gunew MN, Menrath VH. Intramuscular glargine with or without concurrent subcutaneous administration for the treatment of feline diabetic ketoacidosis. *J Vet Emerg Crit Care (San Antonio)*. 2013;23(3):286-290. doi:10.1111/vec.12038
15. Gallagher BR, Mahony OM, Rozanski EA, Buob S, Freeman LM. A pilot study comparing protocol using intermittent administration of glargine and regular insulin to a continuous rate infusion of regular insulin in cats with naturally occurring diabetic ketoacidosis. *J Vet Emerg Crit Care (San Antonio)*. 2015;25(2):234-239. doi:10.1111/vec.12269
16. Liss DJ, Norkus CL. Fluid therapy, electrolyte abnormalities, and acid-base disorders. In: Norkus CL, ed. *Veterinary Technician's Manual for Small Animal Emergency and Critical Care*. 2nd ed. John Wiley & Sons, Inc; 2019:385-416.

CONTINUING EDUCATION

Diabetic Ketoacidosis: Causes, Recognition, and Treatment

LEARNING OBJECTIVE

After reading this article, veterinary nurses should be able to describe how and why patients with diabetes mellitus enter diabetic ketoacidosis (DKA), as well as administer initial therapy.

OVERVIEW

Diabetic ketoacidosis is among the most common endocrine emergencies in cats and dogs and can be fatal without medical intervention. Understanding the pathophysiology of DKA is paramount in successfully treating patients. This article describes the metabolic changes that lead to DKA, the diagnostic hallmarks of DKA, and the emergent treatment of patients presenting with DKA.

This article has been submitted for **RACE approval for 1 hour of continuing education credit** and will be opened for enrollment upon approval. To receive credit, take the test at **vetfolio.com** by searching the name of the article or scanning the QR code below. Free registration is required. Questions and answers online may differ from those below. Tests are valid for 2 years from the date of approval.

1. **Which is not a function of glycogen?**
   a. Glucose utilization
   b. Glycogenolysis
   c. Proteolysis
   d. Lipolysis

2. **Which is a cause of insulin deficiency?**
   a. Obesity
   b. β-cell destruction
   c. Hyperadrenocorticism (Cushing's disease)
   d. Chronic glucocorticoid administration

3. **Which is not a diabetogenic hormone?**
   a. Insulin
   b. Epinephrine
   c. Cortisol
   d. Growth hormone

4. **Urine strips are not accurate for detecting _____.**
   a. β-hydroxybutyrate
   b. Acetoacetate
   c. Acetone
   d. Glucose

5. **During initial bloodwork, which electrolyte will most likely be low?**
   a. Magnesium
   b. Potassium
   c. Sodium
   d. Phosphorus

6. **The number of ketone bodies will start to decrease with fluid therapy.**
   a. True
   b. False

7. **When is the ideal time to institute insulin therapy in a patient with diabetic ketoacidosis?**
   a. Right away
   b. Once hypovolemia is resolved
   c. When the patient is no longer acidotic
   d. Once the ketonemia/ketonuria is resolved

8. **Which is not a proposed insulin administration protocol?**
   a. Regular insulin constant-rate infusion
   b. Subcutaneous and intramuscular glargine
   c. Subcutaneous glargine and intramuscular regular insulin
   d. Subcutaneous regular insulin and intramuscular regular insulin

9. **A patient weighs 25 kg (55 lb) and is receiving 80 mL/h of crystalloid fluids. A veterinarian orders 100 mEq/L of potassium chloride to be added to the fluid bag. Calculate the dose of potassium the patient will receive. Is this a safe dose?**
   a. Yes
   b. No

10. **Most patients presenting with diabetic ketoacidosis have been previously diagnosed with diabetes mellitus.**
    a. True
    b. False

Brief Summary of full Prescribing Information

convenia®

(cefovecin sodium)

Antimicrobial for Subcutaneous Injection in Dogs and Cats Only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS:

Dogs

CONVENIA is indicated for the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

Cats

CONVENIA is indicated for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida.*

DOSAGE AND ADMINISTRATION:

Dogs

CONVENIA should be administered as a single subcutaneous injection of 3.6 mg/lb (8 mg/kg) body weight. A second subcutaneous injection of 3.6 mg/lb (8 mg/kg) may be administered if response to therapy is not complete. The decision for a second injection for any individual dog should take into consideration such factors as progress toward clinical resolution, the susceptibility of the causative organisms, and the integrity of the dog's host-defense mechanisms. Therapeutic drug concentrations after the first injection are maintained for 7 days for *S. intermedius* infections and for 14 days for *S. canis* (Group G) infections. Maximum treatment should not exceed 2 injections.

Cats

CONVENIA should be administered as a single, one-time subcutaneous injection at a dose of 3.6 mg/lb (8 mg/kg) body weight. After an injection of CONVENIA, therapeutic concentrations are maintained for approximately 7 days for *Pasteurella multocida* infections.

General Dosing Information

A sample of the lesion should be obtained for culture and susceptibility testing prior to beginning antimicrobial therapy. Once results become available, continue with appropriate therapy. If acceptable response to treatment is not observed, or if no improvement is seen within 3 to 4 days, then the diagnosis should be re-evaluated and appropriate alternative therapy considered.

CONVENIA may persist in the body for up to 65 days. The effect of remaining concentrations of cefovecin on any subsequent antimicrobial therapies has not been determined. Fluoroquinolone and aminoglycoside antimicrobials have been reported to be compatible with cephalosporin antimicrobial agents.[1,2,3]

Table 1: Dose Table for CONVENIA at 8 mg/kg Body Weight

Weight of Animal	Volume of CONVENIA (3.6 mg/lb or 0.045 mL/lb)
5 lb	0.23 mL
10 lb	0.45 mL
15 lb	0.67 mL
20 lb	0.90 mL
40 lb	1.8 mL
80 lb	3.6 mL

PREPARATION OF SOLUTION FOR INJECTION: To deliver the appropriate dose, aseptically reconstitute CONVENIA with 10 mL Sterile Water for Injection. Shake and allow vial to sit until all material is visually dissolved. The resulting solution contains cefovecin sodium equivalent to 80 mg/mL cefovecin. CONVENIA is light sensitive. The vial should be stored in the original carton and refrigerated when not in use. Use the entire contents of the vial within 56 days of reconstitution.

CONTRAINDICATIONS: CONVENIA is contraindicated in dogs and cats with known allergy to cefovecin or to β-lactam (penicillins and cephalosporins) group antimicrobials. Anaphylaxis has been reported with the use of this product in foreign market experience. If an allergic reaction or anaphylaxis occurs, CONVENIA should not be administered again and appropriate therapy should be instituted. Anaphylaxis may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamine, corticosteroids, and airway management, as clinically indicated. Adverse reactions may require prolonged treatment due to the prolonged systemic drug clearance (65 days).

WARNINGS: Not for use in humans. Keep this and all drugs out of reach of children. Consult a physician in case of accidental human exposure. For subcutaneous use in dogs and cats only. Antimicrobial drugs, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. To minimize the possibility of allergic reactions, those handling such antimicrobials, including cefovecin, are advised to avoid direct contact of the product with the skin and mucous membranes.

PRECAUTIONS: Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant animal pathogens.

The safe use of CONVENIA in dogs or cats less than 4 months of age (see **Animal Safety**) and in breeding or lactating animals has not been determined. Safety has not been established for IM or IV administration. The long-term effects on injection sites have not been determined. CONVENIA is slowly eliminated from the body, approximately 65 days is needed to eliminate 97% of the administered dose from the body. Animals experiencing an adverse reaction may need to be monitored for this duration.

CONVENIA has been shown in an experimental *in vitro* system to result in an increase in free concentrations of carprofen, furosemide, doxycycline and ketoconazole. Concurrent use of these or other drugs that have a high degree of protein-binding (e.g. NSAIDs, propofol, cardiac, anticonvulsant, and behavioral medications) may compete with cefovecin binding and cause adverse reactions.

Positive direct Coombs' test results and false positive reactions for glucose in the urine have been reported during treatment with some cephalosporin antimicrobials. Cephalosporin antimicrobials may also cause falsely elevated urine protein determinations. Some antimicrobials, including cephalosporins, can cause lowered albumin values due to interference with certain testing methods.

Occasionally, cephalosporins and NSAIDs have been associated with myelotoxicity, thereby creating a toxic neutropenia[4]. Other hematological reactions seen with cephalosporins include neutropenia, anemia, hypoprothrombinemia, thrombocytopenia, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), platelet dysfunction and transient increases in serum aminotransferases.

ADVERSE REACTIONS:

Dogs

A total of 320 dogs, ranging in age from 8 weeks to 19 years, were included in a field study safety analysis. Adverse reactions reported in dogs treated with CONVENIA and the active control are summarized in Table 2.

Table 2: Number of Dogs* with Adverse Reactions Reported During the Field Study with CONVENIA

Adverse Reaction	CONVENIA (n=157)	Active Control (n=163)
Lethargy	2	7
Anorexia/Decreased Appetite	5	8
Vomiting	6	12
Diarrhea	6	7
Blood in Feces	1	2
Dehydration	0	1
Flatulence	1	0
Increased Borborygmi	1	0

* Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Mild to moderate elevations in serum gamma glutamyl transferase or serum alanine aminotransferase were noted post-treatment in several of the CONVENIA-treated dogs. No clinical abnormalities were noted with these findings.

One CONVENIA-treated dog in a separate field study experienced diarrhea post-treatment lasting four weeks. The diarrhea resolved.

Cats

A total of 291 cats, ranging in age from 2.4 months (one cat) to 21 years, were included in the field study safety analysis. Adverse reactions reported in cats treated with CONVENIA and the active control are summarized in Table 3.

Table 3: Number of Cats* with Adverse Reactions Reported During the Field Study with CONVENIA.

Adverse Reaction	CONVENIA (n=147)	Active Control (n=144)
Vomiting	10	14
Diarrhea	7	26
Anorexia/Decreased Appetite	6	6
Lethargy	6	6
Hyper/Acting Strange	1	1
Inappropriate Urination	1	0

*Some cats may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Four CONVENIA cases had mildly elevated post-study ALT (one case was elevated pre-study). No clinical abnormalities were noted with these findings.

Twenty-four CONVENIA cases had normal pre-study BUN values and elevated post-study BUN values (37 – 39 mg/dL post-study). There were 6 CONVENIA cases with normal pre- and mildly to moderately elevated post-study creatinine values. Two of these cases also had an elevated post-study BUN. No clinical abnormalities were noted with these findings.

One CONVENIA-treated cat in a separate field study experienced diarrhea post-treatment lasting 42 days. The diarrhea resolved.

FOREIGN MARKET EXPERIENCE: The following adverse events were reported voluntarily during post-approval use of the product in dogs and cats in foreign markets: death, tremors/ataxia, seizures, anaphylaxis, acute pulmonary edema, facial edema, injection site reactions (alopecia, scabs, necrosis, and erythema), hemolytic anemia, salivation, pruritus, lethargy, vomiting, diarrhea, and inappetance.

CONTACT INFORMATION:

For a copy of the Safety Data Sheet or to report adverse reactions, call Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or at www.fda.gov/reportanimalae.

ANIMAL SAFETY:

Dogs

CONVENIA administered to healthy four month old dogs at doses of 12 mg/kg (1.5 X), 36 mg/kg (4.5 X), and 60 mg/kg (7.5 X) every seven days by dorsoscapular subcutaneous injections was well-tolerated for a total of 5 doses. Vomiting and diarrhea were seen in all treatment groups, with the incidence of vomiting and the incidence and duration of diarrhea increasing in a dose-related manner. Injection site irritation and transient edema occurred with increasing frequency in a dose-related manner and with repeat injections. Two injection site reactions included a seroma over the shoulder and swelling lasting > 30 days. Dogs dosed at 36 mg/kg had a significant ($p = 0.0088$) increase in BUN (all means remained within the normal range) compared to the controls. One dog dosed at 60 mg/kg exhibited a glomerulopathy on histopathology, and one dog in this same group had minimal peliosis hepatis.

At an exaggerated dose of 180 mg/kg (22.5X) in dogs, CONVENIA caused some injection site irritation, vocalization and edema. Edema resolved within 8-24 hours.

Cats

CONVENIA administered to healthy four month old cats at doses of 12 mg/kg (1.5 X), 36 mg/kg (4.5 X), and 60 mg/kg (7.5 X) every seven days by dorsoscapular subcutaneous injections was well tolerated for a total of 5 doses. Vomiting and diarrhea were observed in cats, with the incidence of vomiting, and the incidence and duration of diarrhea increasing in a dose-related manner. The mean albumin values for all the CONVENIA-treated cats were significantly lower ($p \leq 0.05$) than the control values (all means remained within the normal range) for all time periods. The mean alkaline phosphatase values in the 60 mg/kg group were significantly higher ($p \leq 0.0291$) than the control values for all time periods. Injection-site irritation and transient edema occurred with increasing frequency in a dose-related manner and with repeat injections. One cat in the 12 mg/kg group had a mild renal tubular and interstitial fibrosis, and one cat in the 12 mg/kg group had mild glomerulosclerosis on histopathology.

At an exaggerated dose of 180 mg/kg (22.5X), CONVENIA was associated with injection site irritation, vocalization and edema. Edema resolved within 8-24 hours. On Day 10, cats had lower mean white blood cell counts compared to the controls. One cat had a small amount of bilirubinuria on Day 10.

STORAGE INFORMATION:

Store the powder and the reconstituted product in the original carton, refrigerated at 2° to 8° C (36° to 46° F). **Use the entire contents of the vial within 56 days of reconstitution**. PROTECT FROM LIGHT. After each use it is important to return the unused portion back to the refrigerator in the original carton. As with other cephalosporins, the color of the solution may vary from clear to amber at reconstitution and may darken over time. If stored as recommended, solution color does not adversely affect potency.

HOW SUPPLIED:

CONVENIA is available as a 10 mL multi-use vial containing 800 milligrams of cefovecin as a lyophilized cake.

REFERENCES:

[1]Pillai SK, Moellering RC, and Eliopoulos GM. 2005. Antimicrobial combinations, pp 365-440. In V. Lorian (ed.) Antibiotics in Laboratory Medicine, 5th ed., Lippincott, Williams, and Wilkins, Philadelphia, PA.

[2]Fish DN, Choi MK, and Jung R: Synergic activity of cephalosporins plus fluoroquinolones against *Pseudomonas aeruginosa* with resistance to one or both drugs. *Journal of Antimicrobial Chemotherapy* (2002) 50, 1045–1049.

[3]Mayer I and Nagy E: Investigation of the synergic effects of aminoglycoside-fluoroquinolone and third-generation cephalosporin combinations against clinical isolates of *Pseudomonas* spp. *Journal of Antimicrobial Chemotherapy* (1999) 43, 651–657.

[4]Birchard SJ and Sherding RG. Saunders Manual of Small Animal Practice, 2nd edition. W.B. Saunders Co. 2000: p. 166.

Approved by FDA under NADA # 141-285

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: July 2022
40039675A&P

TRY THE *purr-fection* OF A ONE-TIME INJECTION

convenia® cefovecin sodium

Fast and effective resolution of common bacterial skin infections in cats

100%

100% Compliance

Feel confident that the cat is getting the full course of recommended medication with one injection.[1]

Quick Treatment

Convenia starts working soon after the injection to kill bacteria fast.[2]

Stress-Free Dosing

Up to 2 weeks of treatment with 1 injection* means your clients don't need to worry about daily pills.[1]

Scan the code to learn more about Convenia

My Zoetis Rewards could help you save on product purchases with every order—learn more at rewards.zoetisus.com.

IMPORTANT SAFETY INFORMATION: People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to Convenia. Do not use in animals with a history of allergic reactions to penicillins or cephalosporins. Side effects for both dogs and cats include vomiting, diarrhea, decreased appetite/anorexia and lethargy. See Brief Summary of prescribing information attached.

*In a US efficacy study, 1 subcutaneous injection of 8 mg/kg Convenia for the treatment of cats with naturally occurring skin infections, wounds, and abscesses was as effective as cefadroxil administered at 22 mg/kg, once daily for 14 days.

References: 1. Six R, Cleaver DM, Lindeman CJ, et al. Effectiveness and safety of cefovecin sodium, an extended-spectrum injectable cephalosporin, in the treatment of cats with abscesses and infected wounds. *J Am Vet Med Assoc.* 2009;234(1):81-87. doi:10.2460/javma.234.1.81 **2.** Stegemann MR, Sherington J, Coati N, Brown SA, Blanchflower S. Pharmacokinetics of cefovecin in cats. *J Vet Pharmacol Ther.* 2006;29(6):513-524. doi:10.1111/j.1365-2885.2006.00795.x

All trademarks are the property of Zoetis Services LLC or a related company or a licensor unless otherwise noted.
© 2024 Zoetis Services LLC. All rights reserved. AIF-00877

zoetis