

# STANDARDS of CARE

## EMERGENCY AND CRITICAL CARE MEDICINE®

FROM THE PUBLISHER OF COMPENDIUM

## MANAGEMENT OF INSULIN OVERDOSE

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**I**nsulin overdose is a serious and potentially fatal complication of insulin therapy in diabetic dogs and cats. Even modest overdoses may result in hospitalization for treatment and monitoring. Morbidity and mortality are due to hypoglycemia, which may range from mild to severe depending on the magnitude of the overdose. Although the problem has been extensively studied in human diabetics, only one study has specifically examined dogs and cats with insulin overdose (see Whitley and associates in Recommended Reading). Treatment is largely supportive and directed at maintaining adequate blood glucose and promoting neurologic recovery.

The clinical signs associated with hypoglycemia are related to autonomic release (neurogenic signs) and central nervous system (CNS) dysfunction (neuroglycopenic signs). A rapid fall in glucose concentration typically provokes an autonomic response. By contrast, neuroglycopenia is classically associated with a gradual and prolonged lowering of blood glucose concentrations. The normal physiologic response to hypoglycemia is inhibition of insulin secretion, stimulation of glucagon secretion, and release of epinephrine, cortisol, and growth hormone. The hormones released in response to hypoglycemia act to oppose insulin action and are collectively referred to as counterregulatory hormones in glucose homeostasis.

In normal animals the counterregulatory response is activated at a glucose concentration of 65–70 mg/dl. Clinical signs are seen at concentrations <50 mg/dl. However, this may not be the case in patients with diabetes mellitus (DM). Glucose homeostasis and the physiologic responses to hypoglycemia are abnormal in humans with Type I (insulin-dependent) diabetes and may be abnormal in dogs and cats as well. In particular, a fall in blood glucose fails to elicit an increase in the glucagon level in Type I diabetics, which impairs counterregulation; later in the disease, when the epinephrine response to hypoglycemia also becomes impaired, the counterregulatory mechanism is completely defective.

Damage to counterregulatory mechanisms can lead to hypoglycemia unawareness. This is a serious problem in humans with diabetes because symptoms that would normally alert them to impending hypoglycemia do not occur. Dogs and cats may or may not develop hypoglycemia unawareness. In many cases, it is likely that the early (neurogenic) signs

of hypoglycemia are misinterpreted, overlooked, or considered unimportant by owners observing their pets at home.

### DIAGNOSTIC CRITERIA

#### Historical Information

##### Gender Predisposition

- **Cats**—Whitley and colleagues found that neutered males were overrepresented in a series of 20 cats with insulin overdose.
- **Dogs**—None.

**Age Predisposition:** Animals of any age that are receiving insulin are at risk for overdose.

**Breed Predisposition:** None.

##### Owner Observations

- Accidental overdose of insulin.
- Weakness, behavioral changes, seizures, or collapse after insulin administration.

### Inside this issue:

#### Peer-Reviewed Articles on

**1** Management of Insulin Overdose

**7** Persistent Hyperglycemia in Diabetic Dogs and Cats

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## Other Historical Considerations/ Predispositions

### General

- Failure to eat a meal after the insulin dose. (Always ask about this when obtaining patient history.)
- Administration of insulin to the wrong animal.
- Misdiagnosis of DM (see Differential Diagnoses).
- Concurrent disease.

### Dogs

SID rather than BID dosing of insulin led to increased episodes of hypoglycemia according to one study.

### Cats

Cats are much more likely to suffer a severe insulin overdose than dogs. This is due to inadvertent administration of massive doses of insulin relative to body weight. In a retrospective study of insulin overdose, the median amount of excessive insulin accidentally given to cats was nearly 2 U/kg, about twice the median value for overdosed dogs.

## Physical Examination Findings

Neurogenic signs appear at blood glucose levels below approximately 50 mg/dl; neuroglycopenic signs dominate when blood glucose levels are below approximately 35 mg/dl. Most dogs and cats with severe hypoglycemia present with multiple neuroglycopenic signs. Hypertension may also be present.

### Neurogenic Signs (Autonomic)

- Tachycardia.
- Muscle fasciculations.
- Tremors.
- Hunger ( $\pm$ ).
- Restlessness.

### Neuroglycopenic Signs (CNS)

- Seizures—The most common presenting complaint reported according to Whitley and others (80% of dogs and 50% of cats). In the study that reported those findings, the median blood glucose in affected dogs and cats was less than 30 mg/dl.
- Bradycardia.
- Prolonged CRT.
- Hypothermia.
- Ataxia.
- Decreased responsiveness.
- Dullness.
- Stupor.
- Coma.
- GI signs (anorexia and vomiting; more common in cats than dogs).
- Vocalization and panting (cats).

## CHECKPOINT

### Control of Glycemia

The degree of glycemic control attempted is directly related to the risk of hypoglycemic episodes in humans with diabetes mellitus. For example, it has been definitively shown in humans that intensive insulin therapy is associated with a several-fold greater risk of hypoglycemia than is standard insulin therapy.

Control of glycemia is a double-edged sword in human diabetics: If extremely tight control of glycemia is maintained, the patient is at risk for multiple episodes of hypoglycemia, which is accompanied by significant morbidity and perhaps mortality. Conversely, failure to maintain adequate control of glycemia is likewise associated with significant morbidity and mortality in the form of diabetic retinopathy, neuropathy, nephropathy, and cardiovascular disease.

Given that the long-term consequences associated with diabetes in humans generally do not occur in diabetic animals, an argument can be made that "loose" control of glycemia is more acceptable for diabetic dogs and cats because it avoids morbidity caused by iatrogenic insulin-induced hypoglycemia.

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## Laboratory Findings

Recommended minimum database—CBC, serum biochemistry panel, and urinalysis. Urine culture is also recommended regardless of the cytologic findings.

### Expected Findings

- Hypoglycemia (normal blood glucose is 70–120 mg/dl [depending on laboratory] in dogs and cats).
- Glucosuria.

### Possible Findings

- Normo- or hyperglycemia (less common, but possible in animals that have received treatment prior to presentation).
- No glucose in urine.
  - In cats, this may indicate spontaneous resolution of transient diabetes.
  - May also indicate blood glucose levels below threshold since bladder was last emptied.

### Nonspecific Findings

- Abnormalities characteristic of DM—Hyperlipidemia, hypokalemia, hyponatremia, dilute urine.
- Abnormalities consistent with other concurrent diseases.

### Other Tests (generally not needed in most cases)

- **Insulin level**—Unnecessary since glucose levels and clinical response determine treatment.
- **Fructosamine levels**—Cannot assess acute hypoglycemia due to insulin overdose.
  - **Exception**—Serum fructosamine level can be normal in a cat suspected of having transient diabetes if the cat has been nearly euglycemic for 10–14 days prior to presenting

### KEY TO COSTS

⌘ indicates relative costs of different diagnostic and treatment regimens.

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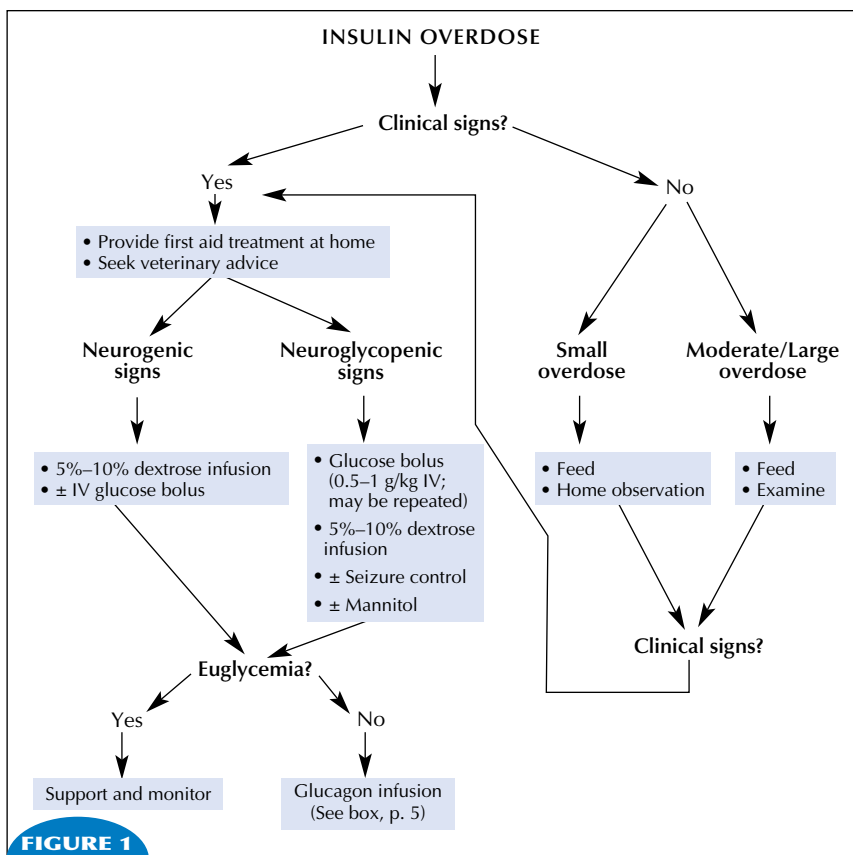


FIGURE 1 Approach to insulin overdose in dogs and cats.

for hypoglycemia. A normal fructosamine level supports but does not prove the clinical diagnosis of transient diabetes, and an elevated level does not eliminate that diagnosis.

### Summary of Diagnostic Criteria

- History of insulin administration.
- Appropriate clinical signs.
- Hypoglycemia.

### Differential Diagnosis

It is rare when hypoglycemia in a diabetic patient is not due to excessive insulin administration. Other causes of hypoglycemia should be considered in diabetic patients when the degree of hypoglycemia seems discordant with the amount of insulin administered (i.e., there is marked hypoglycemia that persists for more than 48 hours following a prescribed dose of insulin), the history of

insulin administration cannot be confirmed, or there are clinical signs inconsistent with hypoglycemia.

- **Seizure-induced hypoglycemia.** Accurate history taking can help differentiate this from hypoglycemia-induced seizures if the animal has been carefully observed.
- **Sepsis** can cause many of the same signs as profound hypoglycemia. Diabetic dogs and cats are at greater risk for bacterial infection than are non-diabetic animals.
- **Insulin-secreting neoplasms** can cause the same signs and laboratory findings as insulin overdose but should be considered an extremely rare cause of hypoglycemia in a diabetic patient.
- **Hepatopathies** can result in symptomatic hypoglycemia, especially in cats and small dogs with low body weight.

- **Large abdominal neoplasms** have been reported to cause hypoglycemia via a mechanism that is not yet determined.
- **Hypoadrenocorticism.**
- **Hypopituitarism** (rare).
- **Polycythemia** (rare).

## TREATMENT RECOMMENDATIONS

In all cases, if overdose is recognized immediately, the owner should feed the animal and/or administer corn syrup. (Also see Figure 1.)

### Mild to Moderate Hypoglycemia \$-\$\$

**Oral Treatment** (in many cases owner can administer)

- Feed animal immediately after insulin overdose.
- Corn syrup (Karo® Syrup)—Apply *liberally* to gingival and buccal surfaces; take care to avoid being bitten.

### Moderate to Severe Hypoglycemia \$-\$\$

**IV Treatment**

**Glucose**—Administer via rapid IV bolus; use an indwelling catheter to alleviate irritation, phlebitis, and hemolysis caused by concentrated dextrose.

- 50% dextrose (0.5 g dextrose/ml) at 1–2 ml/kg (0.5–1 g/kg)

**OR**

10% dextrose (50% dextrose diluted 1:4 with sterile water) at 5–10 ml/kg (0.5–1 g/kg).

- Repeat to endpoint of euglycemia.
- Start constant rate infusion (CRI) of glucose or glucagon (dogs) to maintain euglycemia.

**Glucagon**—Use an indwelling catheter.

- 50 ng/kg has been reported as an effective treatment. Reconstitute 1 mg vial with supplied diluent. Add to 1 L 0.9% NaCl = concentration of 1000 ng/ml (e.g., 5 kg × 50 ng/kg = 250 ng; 250 ng ÷ 1000 ng/ml = 0.25 ml;

can be given using a tuberculin or insulin syringe).

- Repeat to endpoint of euglycemia.
- Start CRI of glucose or glucagon (dogs) to maintain euglycemia.

### Constant Rate Infusion

**Glucose**—Use an indwelling catheter.

- 5% to 10% dextrose added to balanced electrolyte solution. (Addition of glucose slightly increases the osmolality of the electrolyte solution but does not seem to cause clinical problems.)
  - Rate: 10–20 ml/kg/hr in uncomplicated cases.
  - Dose: Variable. Reported median values for total amount of glucose needed to restore euglycemia are >1 g/kg, but individual patients have required up to 20 g/kg. Whitley and colleagues reported that glucose infusion was required for a median time of 18 hours and 8.5 hours to attain euglycemia in dogs and cats, respectively.

- Lower rate gradually while monitoring blood glucose. When animal is hyperglycemic without exogenous glucose, it is safe to stop the infusion.

**Glucagon** (dogs only)

- 1 mg injectable glucagon reconstituted with supplied diluent (see box on p. 5) and then added to 1 L 0.9% NaCl = final concentration of 1 µg/ml or 1000 ng/ml.
  - Rate: 5–10 ng/kg/min via infusion pump (rates up to 37 ng/kg/min have been reported without adverse effects).
  - Dose: Variable; expect 24–36 hours of glucagon CRI in cases of massive insulin overdose.
- Lower rate gradually while monitoring blood glucose. When animal is hyperglycemic without exogenous glucagon administration, it is safe to stop the infusion.

**NOTE:** Monitor blood glucose frequently after stopping glucose or

glucagon infusion to ensure glucose remains elevated.

### Concurrent Treatment

- Cease insulin therapy in diabetic patients with insulin overdose until persistent hyperglycemia develops without the administration of glucose/glucagon.
- Reevaluate:
  - Need: Cats may be transient diabetics and experience spontaneous resolution of disease.
  - Dose: Reduce insulin dose that caused hypoglycemia by at least 25%.
  - Frequency: Consider dividing insulin dose BID in patients that were receiving SID therapy.
  - Insulin: A change in the type of insulin or use of a mixture of insulins (e.g., regular + NPH) may be suitable for some patients.

### Seizure Control \$

Prolonged seizure activity in hypoglycemic animals has clinical consequences that are identical to those resulting from status epilepticus caused by primary neurologic disease, including hyperthermia, permanent neurologic damage, and death.

- Resolution with correction of hypoglycemia is expected.
- Seizures persisting after glucose treatment despite hyper- or euglycemia require examination of other underlying causes. In these cases only, anticonvulsive drugs may be indicated.
  - Diazepam (dogs and cats: 0.5–1.0 mg/kg IV PRN) is a good first choice and can also be used as a CRI (dogs and cats: 0.5 mg/kg/hr IV).
  - Pentobarbital can be used if the response to diazepam is inadequate or if a prolonged period of anesthesia is anticipated. Pentobarbital is given as a slow bolus injection (dogs and cats: 3–15 mg/kg IV

given to effect) or as a CRI (dogs and cats: 0.2–1 mg/kg/hr).

### Supportive Treatment \$–\$\$ Fluid Therapy

Indications—Dehydration/electrolyte imbalance such as potassium.

- An indwelling vascular catheter, preferably placed in a central vein, is best for administering and monitoring fluid therapy.

### Mannitol \$

- Indications—Treatment of elevated intracranial pressure is indicated when signs such as loss of consciousness, opisthotonus, pupillary dilation, abnormal respiration, and bradycardia develop or progress *after* hypoglycemia has been corrected.
- Dose (25% solution; 250 mg/ml) is given slowly over 30 minutes at a rate of 1–2 g/kg IV.
- Administration can cause hyperosmolality, electrolyte disturbances, and volume overload; mannitol must therefore be used with caution in animals that have cardiac disease.

### Patient Monitoring \$–\$\$ Blood Glucose

Check frequently until hypoglycemia is corrected. A portable glucometer is sufficient for this purpose, since the exact blood glucose value is less important than the trend observed over time and presence or absence of clinical signs.

### Neurologic Function

Assess every hour, especially in patients with marked CNS dysfunction due to neuroglycopenia. A full neurologic assessment should be performed after the patient becomes euglycemic.

### Fluid and Electrolyte Balance

Electrolytes should be monitored at least every 12–24 hours, but more frequent measurement is needed in

the early stages of treatment and when aggressive fluid and glucose therapy is likely to disturb fluid and electrolyte balance. Potassium is of particular concern since insulin can promote hypokalemia via its action to drive potassium into cells. Poorly controlled diabetic patients may also have abnormalities of sodium, magnesium, and phosphorus, which must be monitored and supplemented if needed.

### Home Management

Asymptomatic or mildly symptomatic episodes of insulin overdose and hypoglycemia can be managed at home (see box on p. 6), provided the animal can be watched for further signs of hypoglycemia.

- All owners of diabetic animals should receive instructions in the recognition and treatment of hypoglycemia.
- Teach owners to recognize signs of hypoglycemia or massive insulin overdose that cannot be managed adequately at home.

### Milestones/Recovery Time Frames

#### Restoration of Euglycemia/ Hyperglycemia

Diabetic animals will become hyperglycemic again. Cats with transient DM and that no longer require insulin may remain euglycemic.

#### Normal Neurologic Function

Neurologic function should

improve rapidly after hypoglycemia is corrected and the blood glucose concentration remains within the normal range. Persistent neurologic deficits in the face of euglycemia should prompt reevaluation of the original diagnosis, the search for concurrent disease, and consideration of the possibility that neuroglycopenia may have resulted in permanent neurologic damage. Seizures due to hypoglycemia cause generalized neurologic signs. Focal or lateralized signs indicate other abnormalities.

## CONSTANT RATE INFUSION OF GLUCAGON IN DOGS

1. Reconstitute glucagon (1 mg vial) using diluent supplied by the manufacturer.
2. Add reconstituted solution to 1 L bag of 0.9% NaCl. This produces a final concentration of 1000 ng glucagon/ml (1 µg glucagon/ml).
3. A bolus of 50 ng/kg glucagon can be given to patients with severe hypoglycemia.
4. Administer 5–10 ng/kg/min by CRI using an infusion pump.
5. The infusion rate can be increased as needed to maintain blood glucose in the normal range.
6. Monitor blood glucose hourly during the glucagon infusion until the blood glucose concentration stabilizes and within an hour after any change in the infusion rate.
7. Discontinue by gradually decreasing the rate once hyperglycemia occurs.

### ON THE NEWS FRONT

Although a glucagon bolus can be given as emergency treatment to human diabetics with hypoglycemia, glucose remains the standard initial treatment. However, because the increase in blood glucose after administration of a glucose bolus is transient, glucagon infusion is used to maintain glycemia following glucose therapy. Glucagon infusion therapy has only recently been investigated in veterinary patients, but the results are encouraging. Perhaps glucagon therapy will play a greater role in the management of hypoglycemia in the near future.

# GUIDELINES FOR TRIAGE MANAGEMENT OF INSULIN OVERDOSE AND HYPOGLYCEMIA

## Asymptomatic Patients

**Problem:** Suspected insulin overdose.

Occasionally, excess administration of a small amount of insulin is suspected but not certain. For example, an insulin injection may have been repeated because of poor communication between owners. Many of these incidents can be managed at home:

- Owners are instructed to feed the animal immediately.
- Owners should observe the pet for signs of hypoglycemia.
- If signs of hypoglycemia appear, the pet can be examined if necessary.

**Problem:** Known recent insulin overdose.

Occasionally, an owner will realize that an overdose has been administered just after the insulin is injected. Depending on the amount of insulin given, the situation may be managed at home or might require hospitalization. Generally, the following recommendations are applicable:

- The owner should immediately feed the animal or provide glucose by mouth.
- The pet should be transported to the veterinarian for observation and treatment, if needed.

## Symptomatic Patients

**Problem:** Mild signs of hypoglycemia; CNS signs absent.

- May be managed at home by the owner in many cases; advise to use precautions to avoid bites.
- The animal can be fed a normal meal, or immediate care can be provided by rubbing corn syrup on the gingival and buccal surfaces.
- The next dose of insulin should be reduced by 25% to 50% in animals that exhibited symptomatic hypoglycemia after a prescribed dose of insulin.
- The animal should be reexamined if hypoglycemic episodes persist in response to modified insulin therapy.

**Problem:** Severe signs of hypoglycemia or obvious CNS signs.

- Animals with loss of consciousness, frequent or continuous seizure activity, marked weakness, or other signs consistent with marked hypoglycemia cannot be managed at home.
- Instruct owners to provide emergency at-home treatment with oral glucose and immediately transport the pet to the veterinarian.

## Treatment Contraindications

- Oral medications in animals that have a diminished swallow reflex or altered consciousness.
- Infusion of large amounts of glucose-containing fluids, such as D5W, can cause free water overload. As the dextrose in the fluid is metabolized, free water is generated, which can lead to the development of hyponatremia.
- Diazepam and/or phenobarbital in cases of pure insulin overdose with no underlying disease.
- Diazoxide is indicated for treatment of hyperinsulinism due to an insulin-secreting neoplasm (insulinoma) but is not effective for exogenous insulin overdose;

## RESOURCES

**Corn syrup** (Karo® Syrup)—Apply liquid to oral mucous membranes; may be repeated as needed to support glycemia.

**50% dextrose solution** (Abbott Laboratories)—0.5–1 g/kg IV as a 10% solution PRN until euglycemia is restored.

**Glucagon for injection** (Eli Lilly and Co.)—Initial CRI of 5–10 ng/kg/min IV; may be increased as needed to support glycemia. Can administer a 50 ng/kg bolus of glucagon prior to CRI.

this is because the drug acts directly on the insulin-producing cells to inhibit insulin secretion but does not affect any aspect of insulin metabolism or action.

- Somatostatin and somatostatin analogues—Drugs of this class (e.g., octreotide) are contraindicated for the same basic reason as diazoxide. Somatostatin and its synthetic analogues reverse hypoglycemia via direct inhibition of insulin production by normal beta cells and neoplastic insulinoma cells.

## PROGNOSIS

### Favorable Criteria

- A minor overdose of insulin.
- Normal insulin metabolism.
- Short duration of hypoglycemia.
- Minimal clinical signs.

### Unfavorable Criteria

- Massive overdose with prolonged hypoglycemia.
- Intractable seizures.
  - Additional morbidity may occur when permanent neurologic deficits result.
  - In published studies, persistent seizure activity that was unresponsive to anticonvulsant therapy was often cited as a reason for euthanasia of dogs and cats with insulin overdose.

(continued on p. 14)

# PERSISTENT HYPERGLYCEMIA IN DIABETIC DOGS AND CATS

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**N**umerous factors have been identified that could lead to persistent hyperglycemia in treated diabetics. This article will provide guidelines for the step-by-step evaluation and treatment of poorly regulated diabetic dogs and cats.

First, it is important to establish that the dog or cat is actually receiving the prescribed dose of insulin and that the dose is being properly administered. Next, it must be determined whether or not the dog or cat truly has persistent hyperglycemia throughout the day. If the reason for persistent hyperglycemia has not been uncovered by this point, causes of insulin resistance must be investigated. Common causes include obesity, bacterial infection, endocrinopathy, diabetogenic drugs, and any condition associated with elevation of counterregulatory hormones (e.g., stress, trauma, major surgery, pregnancy).

By its simplest definition, insulin resistance is an inadequate biologic response to endogenous or exogenous insulin. However, a definitive diagnosis of insulin resistance is difficult to achieve, and controversy exists regarding the best diagnostic method. Commonly used methods include the glucose clamp, insulin tolerance, and frequent glucose-sampling techniques, all of which are too cumbersome to be practical in most clinical settings. As a result, the diagnosis of insulin resistance is often a clinical one made on the basis of signs, an unusually large insulin requirement, and the presence of a disorder known to cause insulin resistance. For the purposes of this article, insulin resistance is defined using the diagnostic criteria of Peterson (see Recommended Reading), which has become the standard for use in veterinary medicine.

## DIAGNOSTIC CRITERIA

### Historical Information

**Gender Predisposition:** None.

### Age:

- Most diabetic dogs and cats are older than 6 years of age.
- Incidences of diseases that cause insulin resistance peak during middle or old age.

**Breed Predisposition:** None.

### Owner Observations

- Classic signs of diabetes mellitus—Excessive thirst, increased urine

volume and more frequent urination, and increased appetite.

- Increased amounts of insulin are required to control glycemia.
- Glucosuria is detected more frequently or is of a greater magnitude.
- Concurrent disease signs.
- Dermatologic abnormalities due to endocrine conditions.
- Central nervous system signs may occur in dogs or cats with functional pituitary neoplasms.
- Systemic (e.g., lethargy, inappetence, fever) or localized signs (e.g., erythema and swelling or hematuria) due to infection.

### Other Historical Considerations/ Predispositions

- Apparent failure of exogenous insulin to ameliorate or eliminate the clinical signs of diabetes.
- Changes in a diabetic's management schedule (i.e., feeding times, diet change, alterations in timing of insulin administration, different person administering the insulin) that preceded apparent loss of glycemic control.

### Physical Examination Findings

#### General

Vary with underlying cause(s) of hyperglycemia, but include:

- Decreased skin turgor, dry mucous membranes, increased CRT.
- Poor body condition.
- Weight loss.
- Obesity ( $\pm$ ).
- Lethargy.
- Dull hair coat and flaky skin.
- Hepatomegaly (also found in hyperadrenocorticism).

### Diabetes Mellitus

#### Infection ( $\pm$ fever)

- Urinary or reproductive tract: Hematuria, dysuria, vaginal discharge, renal/abdominal tenderness, etc.

- Cardiac murmur: Development of a new murmur or changed characteristics of a previously diagnosed murmur.

## ON THE NEWS FRONT

– **Thiazolidinediones** are a newly developed class of drugs that directly enhance the insulin sensitivity of muscle and adipose tissue.

- Troglitazone, the first thiazolidinedione used clinically to treat human diabetics, has recently been withdrawn from the market due to unacceptable side effects.
- Newer thiazolidinediones in clinical use (e.g., pioglitazone) are purported to have a lower incidence of adverse effects.
- A recent study in healthy cats has established the pharmacokinetic profile of troglitazone in this species, but the drug has not yet been examined in a clinical setting.

– **Vanadium compounds** are derivatives of the trace element vanadium that have insulin-like activity.

- Although the exact mechanism of action is unknown, it is thought that modulation of the phosphorylation/dephosphorylation status of signaling proteins is a possible mechanism by which these compounds might exert their effects.
- A recent abstract reported that vanadium could lower blood glucose and fructosamine in cats with early Type II diabetes.
- Further work is needed before the routine use of vanadium compounds can be recommended.

- Intraabdominal signs: Tenderness, distention, organomegaly, ascites.
- Skin: Pyoderma, abscess, cellulitis, wounds.
- Respiratory tract: Cough, tachypnea, dyspnea, abnormal lung sounds.
- Tooth abscess.

### Dermatologic Disorders

- Thin, inelastic skin with alopecia ± comedones suggests canine hyperadrenocorticism.
- Thickened, flaky skin, dull coat, alopecia, and hyperpigmentation suggest canine hypothyroidism.
- Hyperpigmentation often accompanies insulin resistance in humans but has not been established in dogs and cats.
- Nonpruritic, painful dermal erosions and ulcerations with crusting (especially on feet, muzzle, and perineum) and footpad hyperkeratosis are suggestive of superficial necrolytic dermatitis.

### Skeletal Abnormalities

- Increased body size/weight, broadened skull, flattened facial features, and enlargement of interdental spaces suggest acromegaly.
- Degenerative arthropathy was reported in nearly 50% of acromegalic cats. Organomegaly is also seen in cats.

### Pituitary Neoplasia

- Neurologic signs are varied and include behavioral changes (may be subtle), mental dullness, stupor, seizures, circling, blindness, nystagmus, and cranial nerve abnormalities.

### Laboratory Findings

Abnormalities are likely to reflect the diabetic state and any concurrent illness. Dehydration is frequently detected in diabetic patients presenting for any illness. Parentheses are used below to indicate some possible causes of listed abnormalities. Insulin

resistance cannot be diagnosed on the basis of common laboratory tests.

**Minimum database:** CBC, biochemistry screen, urinalysis, urine culture and sensitivity, and a glucose curve (see box on p. 9).

### Complete Blood Count

- Stress leukogram (stress, hyperadrenocorticism).
- Neutrophilic leukocytosis ± bands (infection).
- Normocytic, normochromic, nonregenerative anemia (canine hypothyroidism).
- Polycythemia (hyperadrenocorticism, feline hyperthyroidism).

### Serum Biochemistry

- Hyperglycemia; serial blood glucose determinations are necessary to document persistent hyperglycemia.
- Azotemia and hyperphosphatemia (renal failure with inability to secrete glucose in urine).
- Increased ALT and ALP (modest elevations are characteristic of many disorders that complicate diabetes).
- Hyponatremia and hypokalemia (diabetes).
- Lipid abnormalities such as hypercholesterolemia and hypertriglyceridemia (common in diabetes and other endocrine disorders).

### Urinalysis

- Dilute urine: Low specific gravity due to glucose-induced osmotic diuresis (diabetes and Cushing's).
- Glucosuria (diabetes): Absence of glucosuria should prompt reevaluation of persistent hyperglycemia diagnosis.
- Cortisol:creatinine ratio: Usually elevated (any disorder causing increased cortisol production).
- Pyuria (infection of urinary or reproductive tract): Bacteriuria without pyuria has been documented in animals with diabetes or hyperadrenocorticism.





- Ketonuria (diabetic ketoacidosis, occasionally found in dogs with hyperadrenocorticism).
- Positive culture: Frequent finding even in cases without microscopic evidence of bacteria (diabetes).

### Other Diagnostic Tests

#### Fructosamine

- May be elevated if hyperglycemia has been present for at least 2 weeks.
- May be especially helpful in cats because levels are not affected by stress hyperglycemia.
- Elevated levels can help uncover unacknowledged management problems in animals that are easily regulated in the clinic but poorly regulated at home.

#### Blood Pressure Measurement \$

- Hypertension occurs in humans as part of a syndrome that also includes obesity and insulin resistance. The degree to which hypertension is directly associated with insulin resistance in dogs and cats is unknown.
- Hypertension is a feature of diabetes and hyperadrenocorticism in dogs and hyperthyroidism in cats that requires treatment once identified.

### Imaging Studies

The following may be helpful for the diagnosis of concurrent disorders in diabetic dogs and cats.

#### Computed Tomography or Magnetic Resonance Imaging \$\$\$-\$\$\$\$

- A recent study reported that all cats suspected of having hyperadrenocorticism or acromegaly also had a pituitary mass that was detectable by CT or MRI.
- CT or MRI can also be useful in the diagnostic workup of dogs with hyperadrenocorticism.

#### Ultrasound Examination \$\$

- Abdominal ultrasonography can be a useful tool for evaluating adrenal gland size in animals suspected of having hyperadrenocorticism.

- The sonographic appearance of the liver in dogs affected with superficial necrolytic dermatitis is virtually pathognomonic for the condition, especially when appropriate clinical signs are present.

- Multiple hypoechoic nodules surrounded by hyperechoic tissue are seen, which gives the hepatic parenchyma a characteristic "Swiss cheese" appearance.

- This corresponds to the nodular hepatopathy that is observed at necropsy.

- Ultrasound is extremely useful for evaluation of animals suspected of having occult infection. The urinary and reproductive tracts, the heart, and abdominal viscera can be visualized and necessary diagnostic samples obtained.

### Summary of Diagnostic Criteria

- History of diabetes mellitus or clinical signs and laboratory findings consistent with diabetes.
- Exogenous insulin partially or completely ineffective for control of the clinical signs of diabetes.

### Differential Diagnoses

#### Incorrect Insulin Therapy

Careful review of the insulin protocol with the owner and observation of the owner's insulin handling and injection techniques are needed before incorrect insulin therapy, due to one or more of the following, can be ruled out as a cause of persistent hyperglycemia:

- Poor owner compliance or failure of owner to understand treatment instructions.
- Errors in the method of administration or dose of insulin, the use of outdated or inactivated insulin, and/or recent changes in diet, insulin type, or dose regimen.

#### Excessive and/or Transient Insulin Activity

- Somogyi phenomenon (the

physiologic rebound hyperglycemia that occurs when hypoglycemia is induced by an excessive dose of exogenous insulin). Rebound hyperglycemia is mediated by the release of counterregulatory hormones (especially glucagon), which are stimulated by hypoglycemia.

- Transient insulin activity. Hyperglycemia may return within several hours following an insulin injection in animals that metabolize insulin rapidly. The maximal effect of exogenous insulin may be diminished, but the most clinically significant effect of rapid insulin metabolism is on the duration of insulin action (Figure 1).

#### Insulin Resistance

Not a specific diagnosis. Recognition of insulin resistance should prompt a diagnostic investigation to identify the underlying disorder. Consider insulin resistance if the following factors are true:

- Technical errors, management problems, and insulin-related problems have been ruled out.
- Persistent hyperglycemia exists despite insulin requirement of >1.5 U/kg/injection.
- Insulin requirement to control hyperglycemia is >2.2 U/kg/injection.

#### Disorders Associated With Insulin Resistance

##### Obesity

- Obesity is probably the most common cause of insulin resistance but is reversible with weight loss and exercise.

##### Bacterial Infection

- The urinary tract, skin, intervertebral disk, cardiac valves, lungs, abdominal organs (especially the liver), and reproductive tract are common sites of infection in diabetic animals.
- Bacterial infection can be difficult to rule out completely, and all

suspect sites should be cultured when possible.

- Infection (with the exception of urinary tract infection) is considered unlikely in an afebrile animal that lacks systemic or localized signs and has a normal leukogram.

### Pancreatitis

- Many dogs and cats (especially the latter) with pancreatitis also have mild to severe hyperglycemia.
- Some animals become permanent diabetics after a bout of pancreatitis, presumably due to destruction of the endocrine elements of the pancreas.
- Insulin resistance has been reported in both acute and chronic forms of pancreatitis in humans. In some instances, insulin resistance persists for months following acute pancreatitis. Little is known regarding the role of insulin resistance as a cause of hyperglycemia in dogs and cats with pancreatitis.
- Pancreatitis can be ruled out by careful physical examination, lack of supportive laboratory changes, and a normal pancreatic ultrasound. However, pancreatitis is difficult to rule out definitively, especially when compatible clinical signs are present.

### Endocrinopathies (See box at right)

#### Hyperadrenocorticism

- Excessive production of adrenal glucocorticoids can lead to insulin resistance.
- Iatrogenic hyperadrenocorticism can produce identical clinical signs.
- Diabetes mellitus and hyperadrenocorticism are common but do not always occur together in dogs. In contrast, nearly 100% of cats with hyperadrenocorticism also have concurrent diabetes mellitus.

#### Thyroid Disorders

- Hyperthyroidism in cats causes

## ENDOCRINE CAUSES OF INSULIN RESISTANCE AND DIABETES MELLITUS

**Obesity**—Obesity is probably the most common cause of insulin resistance, especially in cats, and has been shown to be associated with glucose intolerance. Several hormones with putative roles in the development of insulin resistance have been examined in humans with Type II diabetes, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), leptin, and amylin. Obesity, hypertension, and insulin resistance commonly occur together in humans with Type II diabetes mellitus, but this relationship is not well defined in veterinary patients. Insulin resistance due to obesity is reversible with sufficient weight loss and exercise.

**Hyperadrenocorticism**—Insulin resistance caused by excessive production of adrenal glucocorticoids is a component of Cushing's syndrome. Hyperadrenocorticism can cause hyperglycemia without glucosuria or can produce overt diabetes in some cases. Cushingoid dogs and cats often require massive amounts of insulin to maintain even reasonable control of glycemia. Diabetes mellitus is a common but not universal outcome of hyperadrenocorticism in dogs. In contrast, nearly 100% of cats with hyperadrenocorticism also have concurrent diabetes mellitus.

**Thyroid disorders**—Hyperthyroidism in cats and hypothyroidism in dogs have both been reported to be associated with insulin resistance. Cats with experimental hyperthyroidism had fasting hyperinsulinemia and impaired glucose tolerance, which suggest insulin resistance. The pathophysiology underlying insulin resistance in hypothyroidism may result from the obesity that develops in affected dogs, but elevated growth hormone secretion was recently reported in two hypothyroid dogs.

**Hyperglucagonemia and glucagonoma**—The most common cause of hyperglucagonemia in dogs and cats is diabetes mellitus. Glucagon excess is part and parcel of the clinical diabetic state, and hyperglycemia due solely to insulin deficiency is much less marked than hyperglycemia that develops due to combined insulin deficiency and glucagon excess. Hyperglucagonemia without a discrete glucagon-secreting mass may occur as part of a complex metabolic disorder known as *superficial necrolytic dermatitis* (also called *necrolytic migratory erythema*, *hepatocutaneous syndrome*, and *diabetic dermatopathy*, among many other names). Affected dogs may have skin lesions, diabetes mellitus, hepatic failure, and hypoaminoacidemia. Insulin resistance is marked in some cases. The disease has also been reported in cats. Early reports of the disorder in dogs likened it to the glucagonoma syndrome in humans that results from a functional neuroendocrine tumor, usually in the pancreas. A functional glucagon-secreting mass was previously thought to be the exclusive cause of superficial necrolytic dermatitis, although a functional glucagon-producing tumor was demonstrated in only a minority of dogs with the syndrome.

**Acromegaly**—Many dogs and cats with acromegaly (growth hormone excess) develop insulin resistant diabetes. Diabetes mellitus caused by severe insulin resistance is the most common clinical presentation of acromegalic cats. Acromegaly is most common in male cats and is usually due to oversecretion of growth hormone from a pituitary tumor. In dogs, acromegaly is due to stimulation of growth hormone by progesterone. The site of growth hormone production in the dog is mammary tissue, which is stimulated by exogenous progestins or endogenous progesterone during the luteal phase of the estrous cycle. Thus, intact female dogs are most commonly affected with acromegaly; the condition is extremely unlikely to develop in a neutered female that has not received progesterone compounds or in any male dog.

mild insulin resistance.

- There are several clinical reports of suspected insulin resistance in diabetic dogs with hypothyroidism, which resolved with adequate thyroid hormone supplementation.

#### **Hyperglucagonemia or Glucagonoma**

- Superficial necrolytic dermatitis (hepatocutaneous syndrome) is a metabolic syndrome characterized by hyperglucagonemia and

hypoaminoacidemia. The disease is uncommon in dogs and rare in cats.

- A discrete glucagon-secreting neuroendocrine tumor is uncommon but has been reported in dogs. Diabetes may be present at the time of diagnosis or may develop during the course of the disease in affected dogs.

### Acromegaly

- Secondary insulin-resistant diabetes is common in dogs and cats.
- Diabetes mellitus caused by severe insulin resistance is the most common clinical presentation in affected cats.
  - More common in male cats.
  - Usually due to oversecretion of growth hormone from a pituitary tumor.
- In dogs, acromegaly is due to stimulation of growth hormone by progesterone.
  - Intact female dogs are most commonly affected.
  - The condition is extremely rare in males and occurs in only those neutered females that have received progesterone compounds.

### Hyperlipidemia

- The majority of dogs with primary or secondary hypertriglyceridemia do not develop diabetes mellitus.
- Insulin resistance can be a component of severe hyperlipidemia in diabetic animals.

### Elevated Levels of Counterregulatory Hormones

- Any condition that increases secretion of counterregulatory hormones in diabetic animals (stress, fear, trauma, pregnancy) can result in insulin resistance and diabetic dysregulation.
- Ketoacidosis, cardiac insufficiency, chronic pancreatitis,

renal disease, and hepatic insufficiency can each cause insulin resistance and poor glycemic control.

### Neoplasia

Various types of neoplasia have been associated with insulin resistance in humans. Insulin resistance has been documented in some dogs and cats with cancer and suspected in others. It should be considered a rare possible cause of insulin resistance in dogs and cats

## TREATMENT RECOMMENDATIONS

### Initial Treatment

#### Reestablish Glycemic Control

- Readily accomplished if history identifies a management problem as a source of the persistent hyperglycemia.
- Change type or dose of insulin if hyperglycemia is due to undesirable pharmacologic action of insulin. The changes in insulin type, timing, and dose are made after examination of the glucose curve (Figure 1; also see box on p. 9).
  - **Somogyi effect:** Usually requires a decrease in the dose of insulin by 50%–75% so that hypoglycemia can be avoided. A dose reduction may necessitate a switch to twice-daily injections in some dogs and cats that had previously received a single daily injection.
  - **Rapid insulin metabolism:** A change in the type of insulin used may alleviate this problem (e.g., substituting PZI for NPH), or more frequent doses may be needed.

### Treat Insulin Resistance If Present

This is not always readily accomplished. Resolution of clinical signs and elimination of insulin resistance follow two major treatment principles: control of hyperglycemia and

correction of the underlying cause of insulin resistance.

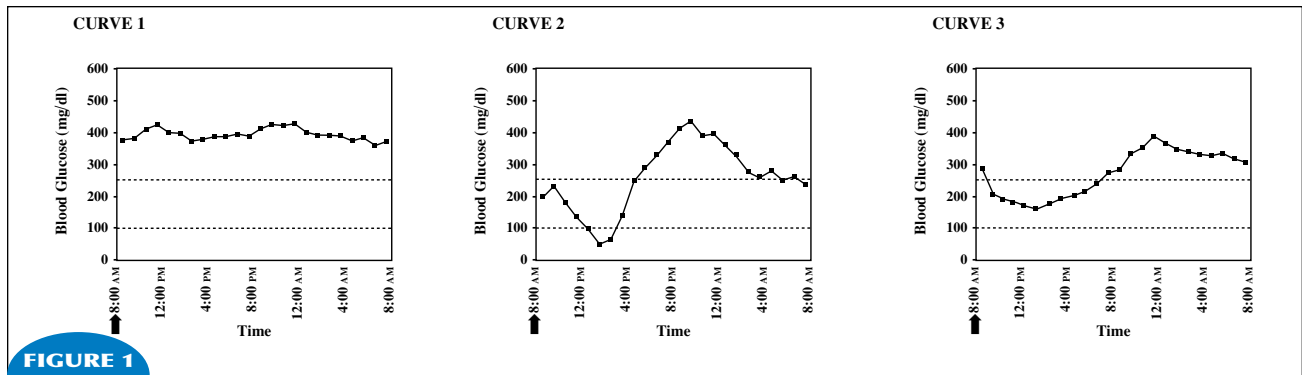
Insulin therapy  $\$$  is used to prevent complications of hyperglycemia and to control clinical signs. However, exogenous insulin does nothing to directly address insulin resistance. Administration of an intermediate-acting insulin twice daily is recommended. Once-daily administration should be avoided. Long-acting insulin preparations (e.g., Ultralente) are generally less effective than preparations with an intermediate duration of action (e.g., NPH). In some patients, a mixture of insulins may improve control. For example, a combination of regular and NPH insulins in a 1:2 ratio has been recommended.

It is important to remain cognizant of the risk of hypoglycemia when large insulin doses are used to control hyperglycemia. Insulin-induced hypoglycemia is more likely to occur as the underlying condition is reversed and insulin resistance is waning. Careful monitoring for signs of hypoglycemia will prevent complications as insulin resistance resolves.

### Steps for Treating Insulin Resistance

Reversal of insulin resistance is accomplished by specific treatment of contributing disorders.

- Discontinue use of drugs associated with insulin resistance, such as glucocorticoids and megestrol acetate.
- Obesity, if present, can be treated with dietary intervention and the institution of an exercise program.
- Bacterial infections are treated with appropriate antibiotics. Initially, broad-spectrum coverage is appropriate when an infection is suspected. Later, a specific antibiotic can be selected based on sensitivity testing results. Surgery may be required for complete resolution when an abscess has formed.
- Endocrine disorders are treated using the medical and surgical



Examples of glucose curves. Arrows indicate time of insulin administration (8:00 AM); dotted lines indicate desired range of glucose for diabetics (100–250 mg/dl).

**Curve 1. Ineffective dose of insulin.** There is no clear onset of insulin activity, the nadir is above 350 mg/dl, and the duration of activity cannot be determined. The difference between the highest and lowest glucose concentration is about 50 mg/dl, but since the nadir is well above 250 mg/dl, the decrease in glucose is irrelevant and the insulin is ineffective. The final interpretation depends on how much insulin the patient received. If the dose was <1.5 U/kg, the patient needs more insulin; if the dose was >2.2 U/kg, insulin resistance is suspected.

**Curve 2. Apparent rapid metabolism due to the Somogyi effect.** The onset of insulin is immediate, the glucose nadir is about 50 mg/dl, and the duration of insulin activity appears to be 8 hr. It would be inappropriate to conclude from this curve that the short duration of action was due to rapid insulin metabolism. The nadir is below the target range, which indicates that insulin is effective, but the nadir is also in the hypoglycemic range (<65 mg/dl). Hypoglycemia stimulates glucagon and epinephrine release, resulting in reactive hyperglycemia. The rise in glucose (which is a physiologic response to hypoglycemia) is unopposed by insulin release (due to the diabetic state), and hyperglycemia ensues. The duration of insulin action appears shortened, but the result is factitious due to the induction of hypoglycemia and reactive hyperglycemia. The insulin dose should be reduced and the glucose curve re-evaluated in 7–10 days.

**Curve 3. Shortened duration of insulin action.** The onset of insulin action is immediate, the nadir occurs at 4 hours and is within the desired range of 80–150 mg/dl, and the duration of insulin activity is about 12 hours. In this case, the dose of insulin is appropriate (the nadir is in the desired range), but the effect is lost after 12 hours. The expected duration of insulin action depends on the type of insulin used. This curve would be inappropriate for a long-acting insulin preparation, such as Ultralente, but might be acceptable for shorter acting preparations like NPH. If the patient is receiving Ultralente, one solution would be to consider switching to another type of insulin; if the patient is receiving NPH, twice-daily administration of the same dose is indicated.

approach that is most suitable for the particular disorder, the patient, and the owner.

- Diabetic animals that are sexually intact should be neutered as part of routine practice to facilitate diabetic control and reduce insulin resistance.
- Modify insulin therapy.

### Alternative/Optional Treatments/Therapy

Pharmaceutical agents that directly ameliorate insulin resistance are available for human patients but are not yet in widespread clinical use for veterinary patients. These agents include the thiazolidinediones and vanadium compounds (see On the News Front).

### Patient Monitoring

The extent to which the patient requires monitoring varies depending on the severity of the patient's condition and the treatment selected. At a minimum, monitoring must include the following:

- **Serum glucose determination \$** can be performed as needed to

follow blood glucose. Frequent monitoring may be needed for animals with moderate to severe hyperglycemia, animals just started on insulin therapy, or under circumstances in which the patient's condition is likely to change rapidly, such as during surgical procedures.

- **Monitoring the insulin requirement \$** is done in the hospital and at home. Animals with insulin resistance typically have high insulin requirements. These requirements can quickly change with reversal of the insulin resistance state. Continued administration of high doses of insulin places the animal at risk for insulin overdose. Clients should be instructed to record the type and dose of insulin administered, so that this information is available should the animal experience hypoglycemia.

- **Monitoring electrolyte balance \$--\$** is important in any diabetic animal. Untreated diabetes commonly causes hyponatremia and hypokalemia. Treated animals can develop hypokalemia, hypophosphatemia, and hypomagnesemia. Abnormalities of acid-base balance are often present as well and must be followed until the patient is stable.

### Home Management

- Careful record keeping and monitoring by the owner and frequent recheck examinations will help to prevent additional errors in diabetes management and allow more rapid recognition and correction of any future problems.
- Insulin-resistant animals are usually managed similarly to uncomplicated diabetics while treatment toward reversing the cause of insulin resistance is ongoing, with the exception that

the insulin dose of insulin-resistant animals may be much higher. Owners will administer insulin, monitor the urine for glucose and ketones, record body weight, and keep a record of the animal's general health.

- Because large amounts of insulin may be needed to control hyperglycemia, special efforts must be made to ensure that owners are aware of the clinical signs of hypoglycemia and the circumstances under which it may occur.
- The owner must not administer medications, supplements, or topical preparations without first consulting the veterinarian. Although the actions of many pharmaceuticals are well studied, the potential for inducing or aggravating insulin resistance may be unknown. The effects, if any, of over-the-counter supplements, herbals, and similar compounds on insulin resistance are generally unpredictable in animals.

### Milestones/Recovery Timeframes

- Immediate improvement should be expected once errors in the management protocol or the insulin therapy regimen are

corrected. If hyperglycemia persists, the validity of the diagnosis must be reevaluated.

- A decrease in the insulin requirement is an indication that the insulin-resistant state is resolving. The rate at which resolution occurs is likely to vary with the underlying cause.

### Treatment Contraindications

- The use of exogenous glucocorticoids is contraindicated in animals with diabetes mellitus.
- Progesterone compounds, such as megestrol acetate, cause the release of growth hormone, which is a counterregulatory hormone that can precipitate or exacerbate insulin resistance. Progesterone administration is contraindicated in diabetic animals.
- Any drug that has the potential for inducing insulin resistance or exacerbating hyperglycemia should be used with caution in diabetic dogs and cats.

### PROGNOSIS

#### Favorable Criteria

- Identification of a management problem as the cause of

persistent hyperglycemia.

- Reversible cause of insulin resistance.
- Early clinical identification of insulin resistance.
- Mild hyperglycemia that is readily controlled with insulin therapy.

### Unfavorable Criteria

- Irreversible or untreatable cause of insulin resistance.
- Patient remains hyperglycemic despite administration of a large amount of insulin.
- Multiple endocrinopathies present or multiple factors identified that contribute to insulin resistance.

### **RECOMMENDED READING**

Nelson RW: Insulin resistance in diabetic dogs and cats, in Bonagura J (ed): *Kirk's Current Veterinary Therapy XII*. Philadelphia, WB Saunders, 1995, pp 390–393.

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Peterson ME: Diagnosis and management of insulin resistance in dogs and cats with diabetes mellitus. *Vet Clin North Am Small Anim Pract* 25(3):69–71, 1995.

### Insulin Overdose (continued from p. 6)

- Repeated episodes of insulin overdose and hypoglycemia due to:
  - Difficulty in regulation of the patient's diabetes.
  - Poor owner compliance.
  - Repeated inability of owner to correctly administer prescribed amount of insulin.

### **RECOMMENDED READING**

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