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Managing the renal cat with concurrent conditions: Kitty kidneys and the kitchen sink

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Canine pancreatitis: A rational approach to diagnosis and therapy

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Chronic renal insufficiency AND ITS ASSOCIATED DISORDERS: KITTY KIDNEYS AND THE KITCHEN SINK

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Renal function declines with increasing age as a normal event. Consequently, renal insufficiency is very common in aging cats. The term *chronic renal insufficiency* is preferable to *chronic renal failure* because this condition is progressive, rather than imminently terminal, and can be treated.

Cats may live for many years after the initial detection of decreased urine specific gravity and elevated blood urea nitrogen (BUN) and serum creatinine, depending on the disease's stage and cause. To grossly lump everything together as chronic renal failure is an oversimplification and disservice to our patients and clients. *Table 1* (page 4) shows the criteria proposed by the International Renal Interest Society in 2006 to characterize renal disease. Staging allows for better communication between practitioners and offers guidelines for the initiation of different therapies. To provide high-quality patient care, practitioners must attempt to carefully define the stage of chronic renal disease, as well as identify and manage any concurrent medical conditions.

HISTORY

Clinical signs of renal insufficiency may include anorexia or inappetence, vomiting, dehydration, weight loss, lethargy, oral ulceration, ptyalism, anemia, social apathy, and constipation. Polyuria and polydipsia are reported less commonly than in dogs, perhaps because of the secretive nature of cats. In assessing the degree of illness, bear in mind that both decreased muscle mass (wasting) of cats with chronic renal insufficiency and concurrent hyperthyroidism will mask the severity of renal insufficiency by lowering serum creatinine levels. Often cats with even moderate renal insufficiency are asymptomatic. We don't need to give them new kidneys—we just need to correct and maintain physiologic parameters that will enable them to enjoy a good quality of life.

Because these patients are older cats, they may have more than one clinical condition. It is not uncommon to have a patient with chronic renal insufficiency that also suffers from pyelonephritis, cardiac disease, or hypertension associated with renal or thyroid disease. Constipation is extremely common in elderly cats. There

may be concurrent inflammatory bowel or small airway disease, diabetes mellitus, neoplasia, or osteoarthritis. These comorbid conditions may complicate our ability to untangle a diagnosis and balance treatments for a specific patient.

DIAGNOSTICS

Following a comprehensive physical examination and consultation (including a fundic examination and blood pressure determination), a minimum database for cats beyond middle age (8 years or older) consists of a complete blood count (CBC) with differential, serum chemistry profile (including T_4), and a complete urinalysis. Cats with renal insufficiency classically have a urine specific gravity of < 1.040, despite some degree of dehydration. Additionally, with progressive decline in function, BUN and creatinine will exceed normal reference values in rehydrated patients. As renal disease progresses, there will be varying changes in urinary protein and potassium levels as well as alterations in serum electrolytes (ionized calcium, phosphorus, and potassium). Anemia also develops due to several causes.

Urinalysis should be collected by cystocentesis. Because pyelonephritis is often subclinical, urine culture and sensitivity testing should be considered in patients with dilute urine (urine specific gravity < 1.020) and white blood cells or trace protein without adequate blood or red blood cells to account for the protein. The method of urine collection (free-catch vs. cystocentesis) affects the interpretation of bacterial colony counts. If the urine is collected by cystocentesis, any number of bacteria is significant. For a free-catch urine sample, bacterial colony counts need to be > 10,000/ml to be significant. Both dilute urine and glucosuria encourage bacterial growth. Additional tests, such as serum fructosamine, can be recommended depending on clinical concerns and diagnostic findings.

MANAGING CHRONIC RENAL DISEASE

Hydration. In cats with chronic renal disease, rehydration is a key component of treatment. Rehydration is critical in perfusing tissues with oxygen and nutrients and scavenging waste. Rehydration aids in acid-base homeostasis. Because cats with renal insufficiency are usually in a state of metabolic acidosis, alkalinizing fluids are the preferred fluid type. In dehydrated patients, increased urea reabsorption due to decreased tubular flow rates may lead to an increase in BUN—even before the glomerular filtration rate is decreased—causing prerenal azotemia. This also causes serum BUN to appear greater than it actually is.

Rehydrate the patient and repeat the blood work before giving a prognosis. With an impaired ability to concentrate urine, despite polydipsia, exogenous fluids are required. Clients commonly administer subcutaneous fluids to cats at home. Increasing oral intake of water can be encouraged through flavoring water, offering milk, and feeding more canned foods. Recirculating water fountains may appeal to some cats.

What about cats with a fragile cardiovascular system? Finding the balance between hydration maintenance to optimize renal function yet not overload cardiovascular capabilities requires fine-tuning through ongoing client communication. This requires frequent reassessment of packed cell volume (PCV), total solids, BUN, and serum creatinine, along with reassessment of body weight, skin elasticity, appetite, and energy.

For the most part, constipation is a clinical sign of dehydration. Cellular water content has priority over fecal water content; thus, primary treatment should address rehydration and the underlying cause of dehydration, rather than stool passage (*e.g.*, with laxatives). Promotility agents, laxatives, osmotic agents, and fiber-enriched diets should be used only after the patient is rehydrated.

Renally-impaired cats with diarrhea from chronic small or large bowel disease have increased fluid losses above their maintenance replacement needs. Attempt to control the underlying cause of the diarrhea. Should corticosteroids be part of therapy (*e.g.*, inflammatory bowel disease or small airway disease), polyuria may worsen. Similarly, for cats with renal disease and diabetes mellitus, address cellular water needs.

Inappetence, nausea, and vomiting. Many cats with uremic gastritis show only signs of partial anorexia or nausea, rather than outright vomiting.

Chronic renal insufficiency
AND ITS ASSOCIATED DISORDERS

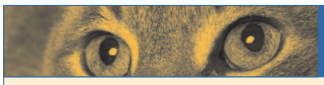

Table 1: Staging chronic renal disease

Recently, the International Renal Interest Society developed a four-level system for staging the continuum of progressive renal disease to use as a guide in diagnosis, prognosis, and treatment. Staging is based on the level of kidney function as determined by creatinine concentrations.

Stage	**I** **Non-azotemic renal disease**	**II** **Mild renal azotemia**	**III** **Moderate renal azotemia**	**IV** **Severe renal azotemia or chronic renal failure**
Creatinine: mg/dL (mmol/L)	< 1.6 mg/dl (< 140 mmol/L)	1.6 to 2.8 mg/dl (140 to 250 mmol/L)	2.8 to 5.0 mg/dl (251 to 440 mmol/L)	> 5.0 mg/dl (> 440 mmol/L)
Clinical signs	None	Possible inappetence, weight loss, polyuria, polydipsia	Usually inappetence, weight loss, polyuria, polydipsia	Uremia, clinically ill
Progression	Stable for long periods of time	Stable for long periods of time	May progress	Fragile
Therapeutic goals	Identify and treat specific primary kidney disease (*e.g.*, acute pyelonephritis, nephrolithiasis)	Identify and treat specific primary kidney disease (*e.g.*, acute pyelonephritis, nephrolithiasis)	Modify progression: phosphorus restriction, omega-3 fatty acids	Ameliorate uremic signs: protein restriction, antiemetics, fluid therapy, appetite stimulation, dialysis
Proteinuria	Classify (see below)	Classify	Classify	Classify
Blood pressure	Classify	Classify	Classify	Classify

Proteinuria
Determined by evaluating sequential urine protein to creatinine (UPC) ratios.
Nonproteinuric = UPC < 0.25
Borderline proteinuria = UPC 0.25 to 0.5; reevaluate after two months
Proteinuria = UPC > 0.4

Classification of blood pressure
NH = nonhypertensive = < 150 mm Hg with no complications
BP = borderline hypertensive = 150 to 160 mm Hg with no complications
Hnc = hypertension no complications = consistent systolic blood pressure values of > 160 mm Hg
Hc = hypertension with extrarenal complications = signs + > 150 mm Hg

H_2-receptor antagonists are underutilized; they function by preventing gastric hydrochloric acid production. Famotidine (0.5 mg/kg orally every 24 to 48 hours) or ranitidine (2 to 3 mg/kg orally every 12 hours) may be considered once serum creatinine is > 2.5 mg/dl (220 µmol/L), even if cats seem nauseated.

Attempt appetite stimulation with cyproheptadine (1 mg/cat orally every 12 hours) or mirtazapine (3 mg/cat orally every 72 hours), which has the added benefit of antiemetic effects. Regardless of concurrent problems, adequate calories need to be ingested. For patients not ingesting adequate calories (*e.g.*, weight loss, poor coat and muscle mass), placement of an esophagostomy or other large-bore feeding tube should be considered.

Hypertension. The incidence of hypertension in cats with renal insufficiency has been reported to be 60%, whereas in cats with hyperthyroidism, the incidence is between 40% to 60%. Evaluation of blood pressure should be considered in all older cats and any ill cats. Cats with chronic renal insufficiency lose the normal autoregulatory capacity of the glomerular arterioles. This not only causes systemic hypertension but also promotes progression of renal insufficiency through glomerular injury.

Treatment of hypertension should be considered in cats withs systolic blood pressure consistently > 180 mm Hg. Amlodipine is the most efficacious agent (0.625 mg/cat orally every 12 to 24 hours, increase gradually over weeks as needed), as it has a direct effect on the peripheral vasculature calcium channels. Angiotensin-converting enzyme (ACE) inhibitors are not as efficacious in decreasing systemic blood pressure. Beta-blockers reduce renin secretion and are similarly unimpressive for treating feline hypertension.

Metabolic acidosis. Cats with chronic renal diseases commonly have metabolic acidosis. This acid-base imbalance promotes severe catabolism of endogenous proteins, exacerbates azotemia regardless of diet, promotes wasting (degradation of protein), inhibits protein synthesis, causes a negative nitrogen balance, and enhances hypokalemia. Acidosis should be aggressively corrected with the use of alkalinizing fluid therapy and H_2-receptor antagonists.

Table 2: Equivalent erythropoietin and darbepoetin dosages*

Erythropoietin (units/week)	Darbepoetin (µg/week)
< 1,500	6.25
1,500 to 2,499	6.25
2,500 to 4,999	12.5
5,000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60

* Total weekly doses

ADDITIONAL TREATMENT OPTIONS

ACE inhibitors. A large, multi-institutional study (the BENRIC study[1]) assessed the effects of benazepril on chronic renal insufficiency in cats. Results of this and other smaller studies[2,3] showed no significant difference in survival time between benazepril or placebo administration. However, for cats with urinary protein loss (urine protein to creatinine ratio), benazepril treatment resulted in longer survival times and better appetite than placebo. Cats without protein-losing glomerulonephropathy may potentially be harmed by this agent because it diverts renal blood, causing a beneficially increased renal interstitial blood flow but a potentially deleterious reduction in GFR. Before diagnosing a protein-losing glomerulonephropathy, sequential urine protein to creatinine ratios should be checked (two over a two-week period) to ensure that proteinuria is persistent, rather than physiologic and transient. Cats with an increased urine protein to creatinine ratio (> 0.4) that are started on benazepril (0.25 to 0.5 mg/kg orally once daily) should be rechecked within three to seven days and have their renal parameters, hydration, body weight, appetite, and overall health monitored. Reevaluate stable patients every two to four months.

Erythropoietin. Erythropoietin causes rapid correction of anemia by stimulating marrow progenitor cells. When PCV is < 20%, consider using erythropoietin at 75 to 100 U/kg subcutaneously three times per week until the PCV is in the low normal range (35%), then reduce dose and frequency to 50

Figure 1: Drug dose adjustment
based on serum creatinine levels

New dose =

$$\frac{\text{old dose } \mathbf{X} \text{ normal serum creatinine level}}{\text{patient's serum creatinine level}}$$

New interval =

$$\frac{\text{old interval } \mathbf{X} \text{ patient's serum creatinine level}}{\text{normal serum creatinine level}}$$

to 75 U/kg subcutaneously two times a week. It is important to monitor PCV for the first 60 to 90 days to detect development of anti-erythropoietin antibodies as noted by a decline in PCV, rather than an increase (at comparable total solids). If this occurs, cease erythropoietin treatment immediately. The cat may be transfusion dependent for two to four months until anti-erythropoietin antibody levels decrease. It is also important to administer iron at the start of the regimen and until the cat's appetite improves. While the risk of anti-erythropoietin antibodies developing exists, most cats will enjoy the benefits of an increased PCV.

Recently, darbepoetin has been receiving attention as an alternative to erythropoietin, and it may be less antigenic and can be given less frequently. The dose is 0.45 µg/kg/week, but it's also possible to convert the current erythropoietin dose (*Table 2*, page 5).

DRUG DOSE ADJUSTMENTS

For a drug that relies on the kidneys for drug clearance, a loss in renal function will proportionately decrease drug excretion. Thus, a 75% loss in renal function results in a 75% loss in renal drug clearance. Dosage adjustments can be made from estimates in the loss of renal function. The most exact method of assessing renal function is to measure creatinine clearance as an estimate of GFR.

A less precise but more practical approach is to make a dose adjustment based on serum creatinine (*Figure 1*). Remember that this type of dose adjustment estimate is risky in geriatric pets, compared with younger pets, because serum creatinine is affected by muscle mass. Therefore, a geriatric animal with decreased muscle mass and renal function may have a falsely low serum creatinine level.

DIETARY RESTRICTION OR SUPPLEMENTATION

Protein. Dietary protein restriction does not ameliorate progression of renal insufficiency in cats based on results in the remnant kidney model in cats.[4] But it's important to note that the remnant kidney model does not reflect or emulate natural disease.

The effectiveness of a therapeutic renal food has been examined in cats with Stages 3 and 4 chronic kidney disease by a randomized, controlled clinical trial.[5] This study examined the benefits of feeding a renal food vs. a standard feline maintenance food. Other than being randomly assigned to either the renal or maintenance food, cats were managed in an identical manner with respect to other treatment interventions. Cats fed the maintenance food had significantly more uremic episodes (22%) than cats fed the renal food (0%). A significant reduction in renal-related mortality was observed in cats fed the renal food. Importantly, significant adverse effects of feeding the renal food were not detected in the study.[6]

However, in acute renal failure, and in mild to moderate chronic renal insufficiency, dietary protein restriction may limit the kidney's compensatory response to injury. Protein restriction may lead to protein malnutrition, which impairs the immunologic response and decreases hemoglobin production, thus promoting anemia, decreasing plasma protein levels, and promoting muscle wasting. Inadequate protein also decreases urinary excretion of magnesium, which may result in calcium phosphate precipitation in the kidneys. Watching for evidence of protein-calorie malnutrition should include monitoring for weight loss, hypoalbuminemia, poor hair coat quality, and muscle wasting.

Dietary treatment of moderate to severe chronic renal insufficiency (serum creatinine > 5 mg/dl, BUN > 75 mg/dl in the rehydrated cat) is not controversial; restriction of both protein and phosphorous are required to avoid uremic complications. Benefits of protein restriction are related to nonrenal effects (toxins affect organs other than kidneys). Using protein sources of high biological value is important. Protein restriction may be especially harmful in renal patients who are inappetent, as a sustained calorie deficit causes body proteins to be catabolized to

Concurrent osteoarthritis, degenerative joint disease, and other disorders

Degenerative joint disorders have been recognized in 90% of geriatric cats[1] and are but one category of many potentially chronic, painful conditions that can occur in these cats. Bacterial cystitis and pyelonephritis are more common in older cats, while the incidence of interstitial, sterile cystitis or inflammatory bowel disease is not different than in younger cats. The likelihood of neoplasia increases with age.

With increasing age come certain risk factors that need to be considered when planning analgesic protocols. Body composition changes in many elderly cats with a decline in interstitial water and possibly a concurrent decrease in muscle mass. Drug dose calculations should, therefore, be made based on an estimate of lean body weight rather than total weight in overweight cats. Attempts to rehydrate to optimize extracellular water components, tissue perfusion, and glomerular filtration should be made. A decrease in renal clearance, as well as any impairment of hepatic function, may alter the pharmacokinetics of therapeutic agents. When liver disease is present, a rough rule of thumb for drugs that require hepatic metabolism is to reduce their dose by 25%. For drugs requiring renal clearance, the frequency of administration should be reduced, or the dose used may be restricted. Cats with chronic renal disease may suffer from uremic gastritis, just as dehydrated cats with reduced gastric blood flow do; in both situations, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of gastric ulceration with or without perforation.

Analgesic choices. The advantages of pure opioid agonists in older cats are their safety, the lack of a ceiling effect allowing dosing to effect, and partial to complete reversibility, if needed. In older patients or those with impaired renal or hepatic function, additional doses of opioid prolong the analgesic effect. Opioids are suitable for use in moderate to severe acute pain or mild to severe chronic pain. Any opioid works in any patient at any age or stage—we just start low and titrate the dose up until the desired effect is seen.

Cats with joint pain are often older patients with concurrent problems. Of most concern are the possible consequences of using NSAIDs in patients predisposed to dehydration, with deleterious effects on their gastric mucosal health or renal function. Additionally, certain NSAIDs may negatively affect proteoglycans synthesis by cartilage. According to in vitro studies, some NSAIDs, including meloxicam and carprofen, do not have this negative effect when used at recommended doses.[2]

Pharmacokinetic and safety data are lacking for long-term NSAID use in cats. The carprofen half-life varies from nine to 40 hours in cats.[3,4] As most NSAIDs have long half-lives in cats when compared with other species, reduce the frequency of administration to avoid toxicity. Remember that individual patients respond differently to the same agent and dose—use the lowest effective dose. Long-term dosing for meloxicam should be based on lean, hydrated weight (day one: 0.1 to 0.2 mg/kg once subcutaneously or orally; days two to four: 0.1 mg/kg orally every 24 hours; long-term: 0.025 mg/kg orally every 48 to 72 hours).[5]

NSAIDs must be used carefully and with renal, hepatic, and coagulation status in mind. While it would be ideal to avoid NSAID use unless renal function is normal, you can enhance the quality of life in patients with concurrent renal disease and chronic pain by ensuring hydration and dosing conservatively. Informing the client of possible side effects is important.

There will never be medical practices that are 100% risk free; good veterinary medicine aims to minimize risks and maximize quality of life for the individual patient.

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supply calories and the nitrogenous end products of this process will further accentuate uremic signs. Inappetence is an indication for avoiding protein-restricted diets.

Phosphorus. It is important to restrict phosphorus in moderately azotemic patients. Phosphorus restriction is more important than protein restriction to survival in the canine remnant kidney model and has been shown to produce renal lesions that are less severe in the feline remnant kidney model. The dose of intestinal phosphate binders cited in the literature may be too low (*e.g.*, aluminum hydroxide initially at 30 to 90 mg/kg per day but dosage must be individualized); increase the dose as necessary to produce consistent, serum phosphorus levels within the normal range. If using calcium-based intestinal phosphate binders, monitor serum calcium levels carefully and switch to or combine them with aluminium-based phosphate binders if necessary. For these agents to be effective, they must be given with food; they act by binding the phosphorus in the ingested food and making it unavailable for absorption.

Potassium. Because hypokalemia may induce a reversible, functional decline in GFR, potassium supplementation is warranted for cats with chronic renal insufficiency and hypokalemia, even in the absence of overt clinical signs. Polyuria results in increased urinary potassium loss as well. Dietary acidification causes intracellular potassium to shift to the extracellular space, raising serum potassium levels but not reflecting total body potassium levels. Thus, metabolic acidosis results in a shift of potassium into the extracellular fluid and should be rectified early in the management of hypokalemia. Potassium supplementation (potassium gluconate at 2 to 4 mEq orally twice a day) may be considered after acidosis is corrected.

Calcitriol. Calcitriol use is still controversial in that some researchers feel that its use is more urgent than others. Calcitriol advocates suggest that it should be started at 2.5 to 3.5 ng/kg/day orally in early renal insufficiency when serum creatinine is 2 to 3 mg/dl, urine specific gravity is compatible with chronic renal insufficiency, and phosphorus is < 6 mg/dl. In these patients, the parathyroid hormone levels are often normal; calcitriol is used to prevent hormone levels from increasing to slow progression of the chronic renal insufficiency and prevent clinical signs related to parathyroid hormone toxicity. In patients with a serum creatinine of > 3 mg/dl and serum phosphorous of < 6 mg/dl, the dose is 3.5 ng/kg/day orally. A baseline parathyroid hormone measurement in these patients is useful because the levels are commonly elevated and may require higher doses of calcitriol. It is imperative to have good client compliance—carefully monitor ionized calcium and parathyroid hormone levels. The Ca times P product must be < 60.

CONCLUSION

Chronic renal insufficiency is progressive and can be treated. To provide high-quality care, veterinarians must carefully define the stage of chronic renal disease by taking a thorough history, performing a comprehensive physical examination, and running indicated laboratory testing. Cats may live for many years after the disease is detected with proper hydration and management of concurrent medical conditions.

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Managing the OBESE DIABETIC CAT

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Diabetes mellitus is one of the most common feline endocrine diseases, affecting one in every 200 to 300 cats.[1] Despite the increasing frequency of the disease, treatment of diabetic cats can be frustrating, and many patients experience such complications as hypoglycemia and progressive neuropathy.[2-7] The latest clinical and histologic evidence now suggests that type 2 diabetes mellitus is the most common form of diabetes affecting cats and people.[2-4]

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

In cats, diabetes mellitus is characterized by an impaired ability to secrete insulin following a glucose stimulus and is caused by both a defect in pancreatic beta cells and by peripheral insulin resistance.[2-4] It is now recognized that these classic metabolic abnormalities found in type 2 diabetes mellitus may be consequences of abnormal amyloid production by pancreatic cells and by secretion of hormones from adipose tissue.[2-4]

Both the amount and distribution of adipose tissue play a role in insulin resistance and other obesity-related disorders. Resistin, a hormone produced by central adipose tissue and certain gastrointestinal cells, is an important link between adipose tissue and glucose homeostasis. Studies have shown that resistin increases hepatic glucose output even when insulin levels are high. This is the earliest change in type 2 diabetic people and cats. Adipose tissue also secretes the hormone adiponectin, which directly increases fatty acid transport, oxidation, and dissipation in skeletal muscle and, therefore, results in reduced levels of intramyocellular lipids, which improve insulin signaling. Adiponectin also increases hepatic insulin sensitivity either directly or indirectly by lowering circulating lipids via its action on muscle. The synthesis and secretion of adiponectin is reduced by caloric excess, and adiponectin administration results in improved insulin sensitivity and glucose tolerance associated with obesity. Finally, leptin resistance is found in early type 2 diabetes as a result of an increase in visceral abdominal tissue.

Obesity and early type 2 diabetes also affect insulin sensitivity. Obese cats have low GLUT-4 (insulin sensitive glucose transporter) expression in both muscle and adipose tissue; however, the expression of GLUT-1 (insulin insensitive glucose transporter) is similar in lean and obese cats.[8] A decrease in GLUT-4 transporters occurs early in

Managing the OBESE DIABETIC CAT

Table 1: Protocol for monitoring urine glucose after diagnosis of type 2 diabetes mellitus

1. Change the diet to Purina Veterinary Diets DM, and feed the prescribed amount twice daily in equal meals.
2. Give the prescribed amount of insulin twice daily subcutaneously. The ideal place for insulin injection is on the abdomen, but the lower back and sides of the chest and abdomen are also acceptable.
3. OR your veterinarian may prescribe an oral hypoglycemic agent, such as glipizide.
4. Monitor urine sugar using the GLUCOTEST system. As the urine sugar drops, you will see less color change on the strips. When the urine sugar becomes negative for two days in a row, decrease the insulin by the following schedule:
    - 2 units insulin twice daily starting dose
    - negative urine glucose x 2 days, decrease to 1 unit twice daily
    - negative urine glucose x 2 days, decrease to 1 unit once daily
    - negative urine glucose x 2 days, discontinue insulin completely
5. Insulin dosages should NEVER be increased based on urine sugar.
6. Visit your veterinarian for check-ups and blood work (fructosamine, chemistry profile) once monthly.

the course of diabetes development and could help identify which cats will develop clinical disease.

Insulin secretion is affected early in the course of type 2 diabetes mellitus in people, particularly glucose-mediated insulin secretion. The glucose transporter in pancreatic beta cells is GLUT-2. A decreased expression of these transporters causes a loss of the first phase of insulin secretion but normal second phase of insulin secretion similar to what is seen in later stages of obesity in cats (and people). Insulin resistance in beta cells may also lead to a decrease in insulin secretion.

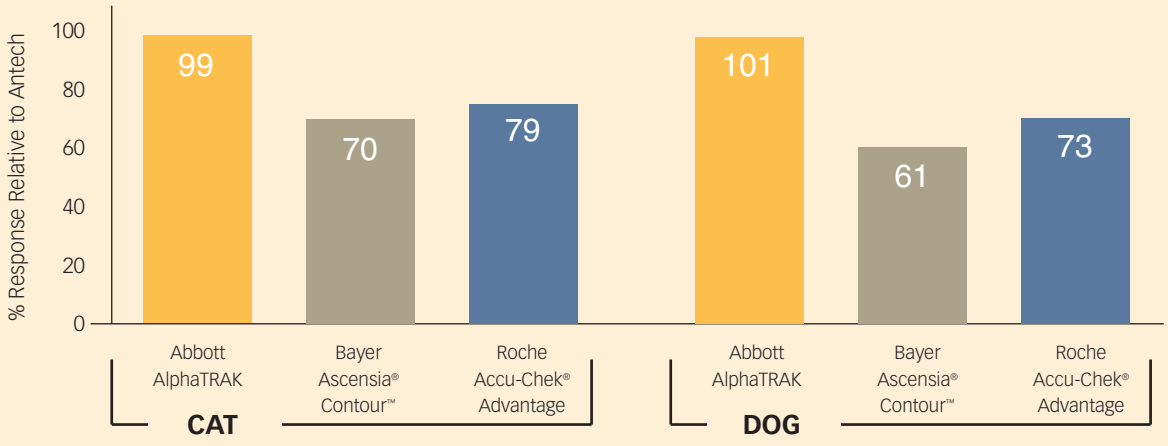
In some forms of diabetes, a mutation of the glucokinase enzyme may lead to impaired insulin secretion in people. In animals and people, glucokinase converts glucose to glycogen for storage in the liver and is important in "mopping up" excess postprandial glucose. Normal cats that are deficient in glucokinase are similar to diabetic people in which glucokinase levels drop precipitously with persistent hyperglycemia from type 2 diabetes mellitus.

DIAGNOSIS

The early clinical signs of diabetes are almost nonexistent. In fact, the only signs that a cat may be developing type 2 diabetes mellitus are obesity and an increased appetite (from leptin resistance). As the disease progresses to affect insulin secretion and to cause insulin resistance, diabetic neuropathy and possibly nephropathy begin to appear. Diabetic neuropathy typically affects the hind limbs and can cause inappropriate elimination. This can be caused by an inability to climb in and out of the litter box, particularly if the box has tall sides, or it's not easily accessible (*e.g.*, placed far away or at the bottom or top of stairs). Cats affected with diabetic neuropathy also can have trouble jumping onto high surfaces, such as counters and beds. Finally, diabetic neuropathy in people is associated with a variety of paresthesias and an inability to sense changes in surface temperatures. This condition may lead to irritability in affected cats. In one study, clinical and nonclinical diabetic cats all suffered from subclinical forms of diabetic neuropathy as evidenced by impaired motor and sensory peripheral nerve conduction.[7]

The late signs of diabetes mellitus are easily identified. As blood glucose concentrations exceed the renal threshold (which may be as high as 350 mg/dl in some cats), polyuria and secondary polydipsia become the primary clinical signs. Weight loss begins as a result of calories lost in glucose-laden urine. Nonspecific gastrointestinal signs, such as anorexia and diarrhea, develop intermittently in diabetic cats. This is perhaps a result of an autonomic neuropathy. As the diabetes progresses, ketosis and hyperosmolality lead to vomiting and severe dehydration, and the cat

Figure 1: Correlation of blood glucose test results between handheld monitors and clinical laboratory analysis*



* Source: Abbott Animal Health. Diabetes monitoring product. Available at: www.abbottanimalhealth.com/vetProfessionals/products/DiabetesMonitoring. Accessed March 26, 2007.

will present in a mixed hyperosmolar ketotic crisis.

For diabetic patients, clinical pathology abnormalities include hyperglycemia, glucosuria, and elevated serum fructosamine. Unfortunately, cats are susceptible to stress-induced hyperglycemia, which makes interpretation of isolated elevated serum glucose values difficult. In general, an elevated blood glucose (> 130 mg/dl or 7 mmol/L) and a normal fructosamine (< 300 µmol/L) is consistent with stress-induced hyperglycemia. In contrast, an increase in both glucose and fructosamine would be consistent with early type 2 diabetes mellitus. Other common findings on the serum chemistry profile include elevations of serum alkaline phosphatase and alanine amino transferase activities as a result of reactive hepatopathy and hepatic lipidosis, hyperlipidemia (triglycerides and cholesterol), and azotemia (either prerenal due to dehydration or renal associated with diabetic nephropathy). In cats with diabetic nephropathy, urine specific gravity may be decreased, and proteinuria is common. The presence of glucosuria may or may not be helpful in most situations, as stress can result in glucosuria.

TREATMENT

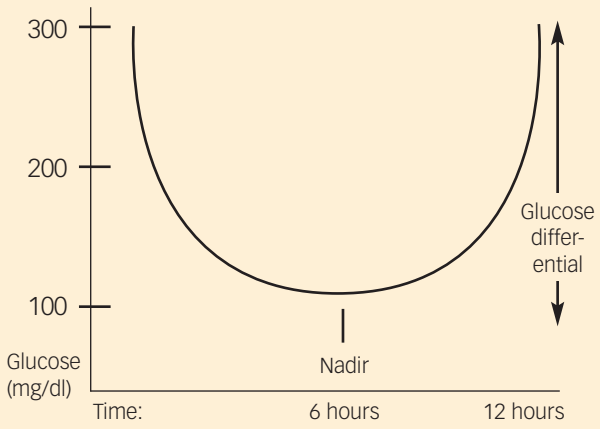
Diet

The cat is an obligate carnivore; therefore, amino acids, rather than glucose, are the signal for insulin release in cats.[10] In fact, a recent study demonstrated more effective assessment of insulin reserve in cats using the arginine response test rather than a glucose tolerance test.[11] Another unusual aspect of feline metabolism is the increase in hepatic gluconeogenesis seen after a normal meal. Normal cats maintain essential glucose requirements from gluconeogenic precursors (*i.e.*, amino acids) rather than dietary carbohydrates. As a result, cats can maintain normal blood glucose concentrations even when deprived of food for more than 72 hours,[10] and feeding has very little effect on blood glucose concentrations in normal cats.[2,12] When type 2 diabetes occurs in cats, these metabolic adaptations to a carnivorous diet can become harmful, leading to severe protein catabolism, and feeding a diet rich in carbohydrates may exacerbate hyperglycemia and protein wasting in these diabetic cats.

People with type 2 diabetes mellitus are often instructed to restrict excess dietary carbohydrates, such as potatoes and bread, and to control obesity by caloric restriction.[13] Furthermore, people with type 2 diabetes have been shown to have improved glycemic control and improvement in protein catabolism during weight loss when a low-energy diet (high-protein) was combined with oral hypoglycemic therapy.[14]

A low-carbohydrate, high-protein diet that is similar to a cat's natural diet (*e.g.*, mice) may ameliorate

Figure 2: Ideal blood glucose curve



- The ideal blood glucose curve has a glucose nadir (the lowest blood glucose concentration on the curve) of 80 to 120 mg/dl (4 to 7 mmol/L).
- The time of the glucose nadir indicates peak insulin action, and the nadir should occur approximately halfway through the dosing interval. For example, if insulin is administered every 12 hours, the nadir should fall five to six hours after the dose.
- The glucose differential is the difference between the absolute concentration of glucose at the nadir and the absolute concentration of glucose before the next insulin dose. Mid-day blood glucose concentrations should be less than 180 mg/dl in cats with well-controlled diabetes.

some of the abnormalities associated with diabetes mellitus in the cat. Initial studies using a canned high-protein/low-carbohydrate diet and the starch blocker acarbose have shown that in 58% of cats insulin injections could be discontinued, and those with continued insulin requirements could be regulated on a much lower dosage (1U twice a day total).[15] Comparison of canned high-fiber versus low-carbohydrate diets showed that cats fed low-carbohydrate diets were twice as likely to no longer require insulin injections.[16]

Another study examining clinical cases of diabetes mellitus in cats fed a high-protein, low-carbohydrate food (Purina Veterinary Diets DM) showed that insulin dosage could be decreased by 50%, and 25% to 30% of cats could discontinue insulin altogether.[17] Caution should be used when initially changing from dry to canned foods, as insulin requirements may decrease dramatically. A reduction in insulin dosage may be required. Weight reduction also decreases insulin resistance, and cats should be fed no more than 50 kcal/kg of ideal body weight in two equal meals per day.

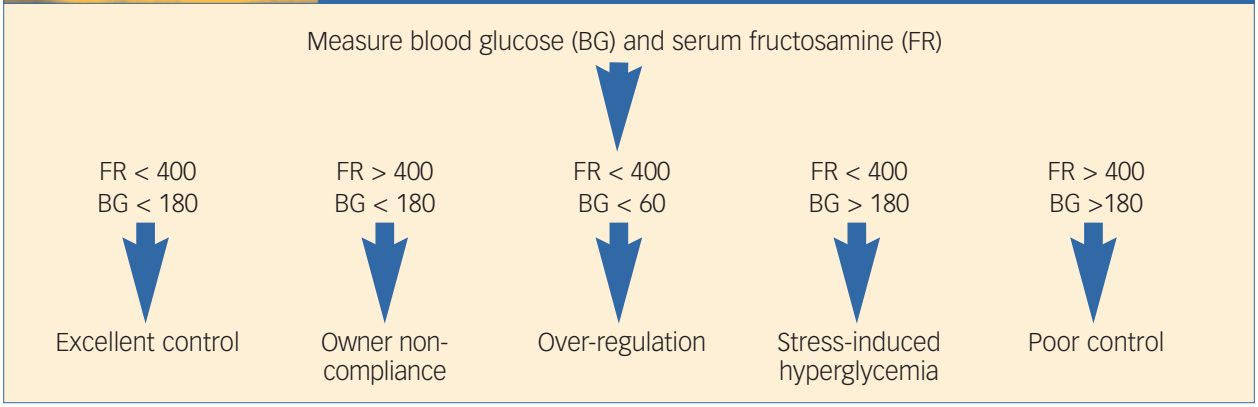
Oral hypoglycemics

Indications for oral hypoglycemic therapy in type 2 diabetic cats include normal or increased body weight, lack of ketonuria, no underlying disease (pancreatitis, pancreatic tumor), history of diabetogenic medications, and the owners' willingness to administer oral medication rather than an injection. Diet should consist of low-carbohydrate/high-protein foods only.

Cats with early type 2 diabetes are most likely to respond to any oral hypoglycemic agent. Sulfonylureas, such as glipizide, increase insulin secretion and improve insulin resistance. Because they provoke insulin release, sulfonylureas may promote progression of pancreatic amyloidosis. In cats, glipizide has been used to successfully treat diabetes mellitus at a dosage of 2.5 mg twice daily when combined with a high-protein, low-carbohydrate diet. The patient is evaluated weekly (urine glucose) or every two to four weeks (fructosamine) for a period of two to four months. Gastrointestinal side effects, which occur in about 15% of cats treated with glipizide, usually resolve when the drug is administered with food.[18] A new sulfonylurea, glimepiride (Amaryl—Aventis Pharmaceuticals) has recently entered the human market; this compound has fewer side effects than glipizide and may be dosed once daily at 2 mg per cat.

Alpha-glucosidase inhibitors impair glucose absorption from the intestine by decreasing fiber digestion and the resulting glucose production from food sources.[19] These medications are not absorbed systemically and may be used in conjunction with other oral hypoglycemics or insulin. Acarbose may be used as the sole initial therapy in obese prediabetic patients suffering from insulin resistance or as adjunct therapy with sulfonylureas or insulin to enhance the hypoglycemic effect in patients with diabetes mellitus. I have had experience using acarbose at a dosage of 12.5 mg/cat twice a day administered with a meal. The glucose-lowering effect of acarbose alone is mild with blood glucose concentrations decreasing only into the 250 to 300 mg/dl (14 to 17 mmol/L) range. However, acarbose is an excellent agent when combined with

Figure 3: Algorithm: Monitoring with serum fructosamine



insulin to improve glycemic control. Side effects are rare with appropriate diet adjustments but, at high dosages, may include flatulence, loose stool, and diarrhea.

Insulin

Although all mammalian insulin is structurally similar, small differences in amino acid sequences may be found between species. Mammalian insulin is composed of 51 amino acids arranged in two polypeptide chains.[20] The A-chain contains 21 amino acids and the B chain contains 30 amino acids. PZI insulin is available as a beef-pork formulation (IDEXX Pharmaceuticals). Pork Lente insulin is available as Vetsulin (Intervet), but Ultralente is no longer available from any company. When contemplating a change in insulin source, consider that different types and brands have different pharmacologic properties. Synthetic insulins, such as Lantus (glargine), have been developed for use in human medicine. Preliminary research on glargine suggests that it has some advantages over PZI insulin in cats. In fact, recent studies have shown that a combination of glargine and a low-carbohydrate, high-protein diet resulted in 100% remission of insulin dependence in newly diagnosed cats.

Initial insulin doses range from 0.2 to 0.5 U/kg; however, most cats are readily managed on two units twice daily as a starting dose.[22] If intermediate-acting insulin is used, it must be administered to cats twice daily because of its short duration of action. If PZI insulin is used, a once-daily starting dose of one to three units per cat is often recommended. Glargine (Lantus insulin) should be used cautiously in cats to avoid hypoglycemia. A starting dose of one to two units twice daily is recommended, with careful blood or urine monitoring, to avoid hypoglycemic episodes.[22]

The injection site should be discussed with pet owners, as insulin absorption differs from site to site. In animals, the back of the neck (scruff) is commonly used for insulin injection. However, this site is not recommended because of lack of blood flow and the potential for increased fibrosis caused by repeated injections at this site. Instead, the recommended injection sites are along the lateral abdomen and thorax. The owner should rotate the site of injection daily. Many commercially available pamphlets outline injection techniques, feeding, and hypoglycemic episode management, and they provide a log sheet for owners to record food intake, clinical signs, urine glucose measurements, and insulin dosages.

MONITORING DIABETIC CATS

Urine glucose

Urine glucose monitoring may be performed at home by owners, is not affected by stress, and may indicate insulin-induced hyperglycemia (Somogyi effect) indicated by high urine glucose on repeated morning samples. Urine glucose is a measure of trends in blood glucose and should not be used alone to adjust insulin dosages. However, urine glucose should decrease to trace or one plus with appropriate therapy. Consistently high urine glucose indicates the need for blood glucose evaluation. It is

vitally important that the client monitor the urine glucose when the cat is ready to go off insulin. This is best accomplished using the Glucotest system, a home urine glucose monitoring system for cats that allows clients to wean their pets off of insulin. The Glucotest packets can be sprinkled in the litter pan over premium clumping litter and checked daily for color change. Using this monitoring method to adjust diabetes treatment allows for approximately 70% of cats to be managed with little or no insulin (*Table 1*, page 10).

Blood glucose

Glucose monitors designed for home monitoring in people are inexpensive, accurate, rapid, and require only a drop of blood. Although reasonably accurate in the blood glucose range of 60 to 120 mg/dl (4 to 12.5 mmol/L), these monitors are designed to read lower than the actual value as glucose approaches the hypoglycemic range. Above 120 mg/dl, human monitors are not accurate. Such factors as altitude, oxygen therapy, patient hematocrit, shock, dehydration, severe infection, and out-of-date or improperly stored test strips, can all affect the monitors' accuracy. Whole blood glucose concentrations are lower than serum glucose concentrations (because of the metabolism of glucose by red blood cells in whole blood), so veterinarians should consult the monitor manufacturer to determine suitability for feline patients. A veterinary glucose monitor marketed as the Abbott AlphaTRAK has the highest correlation to clinical laboratory sample glucose analysis, as shown in *Figure 1* (page 11). The Bayer Ascensia Contour and the Roche Accu-Chek Advantage are both excellent human monitors, but fall short of the accuracy of the Abbott product when used in animals.

It is very rare to obtain a perfect glucose curve in a single patient. In fact, blood glucose curves are good for identifying trends in blood glucose during the day and not very helpful in cats. Blood glucose curves contain information vital to maintaining or adjusting insulin dosages (*Figure 2*, page 12).

The glucose nadir is the lowest concentration of blood glucose on the curve and should occur approximately halfway through the dosing interval. For example, if insulin is administered every 12 hours, the nadir should fall 5 to 6 hours after the insulin dose. The time of the glucose nadir indicates the time of peak insulin action, and the ideal blood glucose curve should have a nadir between 100 to 150 mg/dl (5 to 8 mmol/L).

The duration of insulin action is related to both the time of the glucose nadir and the absolute concentration of the glucose nadir, in that you cannot determine insulin duration until achieving the target glucose nadir concentration of 80 to 120 mg/dl (4 to 7 mmol/L). If the target glucose nadir is achieved approximately halfway through the dosing interval, the duration of action of insulin and, thus, the type of insulin used, should be adequate.

The glucose differential is the difference between the absolute concentration of glucose at the nadir and the absolute concentration of glucose before the next insulin dose. The glucose differential should be less than 150 to 200 mg/dl (8 to 11 mmol/L) in cats.

Generally, atypical blood glucose curves can be differentiated by the curve's characteristics and the insulin dosage (per dosing interval). If the patient is receiving > 2.2 U/kg of insulin per dose, insulin resistance should be investigated. Causes of insulin resistance in cats can include hyperthyroidism, hyperadrenocorticism, acromegaly, drug therapy, and infections. If the patient is receiving < 2.2 U/kg per dose, the blood glucose curve usually is indicative of one of the following: insufficient dosage of insulin, short duration of action of insulin, insulin-induced hypoglycemic hyperglycemia (Somogyi effect), or insulin overlap seen with prolonged insulin action. Corrective actions include, respectively, increasing the insulin dose, changing to a longer acting insulin or twice-daily insulin regimen, reduction of the insulin dose by 25%, or changing to a shorter-duration insulin or a mixture of insulin types.

Glycosylated blood proteins

Glycosylated blood proteins are indicative of mean glucose concentrations in serum over an extended period of time and may be used to monitor long-term insulin therapy. These proteins are particularly useful in monitoring diabetic cats that may be stressed by hospitalization and serial blood glucose curves. As

plasma glucose concentrations increase, glycosylation of hemoglobin and serum proteins increases proportionately. Glycosylation of serum proteins, such as albumin, forms fructosamine. Because albumin has a shorter life span than hemoglobin, fructosamine concentrations reflect more recent changes (one to three weeks) in serum glucose concentrations than glycosylated hemoglobin concentrations. Fructosamine concentrations less than 400 to 450 µmol/L are associated with good to excellent glycemic control; concentrations of 450 to 550 µmol/L indicate fair to good control; and serum fructosamine greater than 550 µmol/L indicates poor glycemic control (*Figure 3*, page 13). Relative changes in serum fructosamine may be more helpful than absolute values in some cases. It is often helpful to interpret the serum fructosamine in concert with mid-day blood glucose concentrations.

CONCLUSION

Obesity is the primary cause of early type 2 diabetes mellitus in cats. This relationship of increased diabetogenic hormones, such as resistin and leptin, is important in the pathogenesis of insulin resistance and eventual clinical signs of diabetes. Early diagnosis coupled with strict dietary regulation will result in improvement of the diabetic state and restoration of normal patterns of insulin secretion. In cats with more advanced early type 2 diabetes mellitus, the use of oral hypoglycemic agents along with a high-protein, low-carbohydrate diet will result in adequate diabetic control. Diabetic cats should be monitored for reversal of glucose toxicity and insulin dependence using at-home glucose monitoring, blood glucose curves (in some cases), and serum fructosamine.

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Managing the diabetic cat
WITH CONCURRENT GASTROINTESTINAL DISEASE

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The uncomplicated diabetic cat can be managed with diet and oral hypoglycemic therapy or insulin. Even obese diabetic cats often recover from their insulin-dependent state following a short course of an insulin, such as glargine. However, a minority of diabetic cats experience progressive disease that requires dietary changes, insulin, and ancillary therapy to control such concurrent conditions as anorexia, vomiting, diarrhea, and weight loss.

CONCURRENT GASTROINTESTINAL DISEASE

Conditions considered common in human diabetics, such as oral candidiasis and esophageal abnormalities, are uncommon in cats. Gastritis, particularly infectious gastritis, is also common in people. However, it is unclear if diabetic cats vomit as a result of infectious or inflammatory gastritis or if the vomiting is associated with systemic disease. Constipation—the most common gastrointestinal complaint in people with type 2 diabetes mellitus—occurs less frequently in diabetic cats and can be caused by dehydration or abnormalities in colonic motility resulting from autonomic neuropathy. Treatment should consist of regulating the diabetes mellitus, providing fluids for dehydration, evacuating the colon with cleansing enemas, and possibly using a gastrointestinal prokinetic agent, such as cisapride. Lactulose may be used as a laxative but could contribute to dehydration.

Nonspecific diarrhea is a common finding in both cats and humans. The pathogenesis of diarrhea in diabetic people is poorly understood, but altered motility, increased intestinal secretion, exocrine pancreatic insufficiency, gluten-induced enteropathy, and bacterial overgrowth are considered possible causes. Bacterial overgrowth seems a likely candidate, as diarrhea in human patients often responds to antibiotics and probiotic therapy.

The most common pancreatic disorder in cats is chronic relapsing pancreatitis. Diabetic cats, particularly those that do not respond to insulin therapy, should be screened for chronic pancreatic disease (see *Canine pancreatitis: A rational approach to diagnosis and therapy* on page 19 for details on appropriate testing). Because inflammatory

bowel disease, pancreatitis, and cholangiohepatitis are often observed together, these conditions are considered a "triad." Its pathogenesis is not well understood; however, bacterial overgrowth and inflammation secondary to this overgrowth has been suggested as a possible cause of "triaditis." In some cases, chronic pancreatitis may result in exocrine pancreatic insufficiency, which requires the replacement of pancreatic enzymes as a dietary supplement.

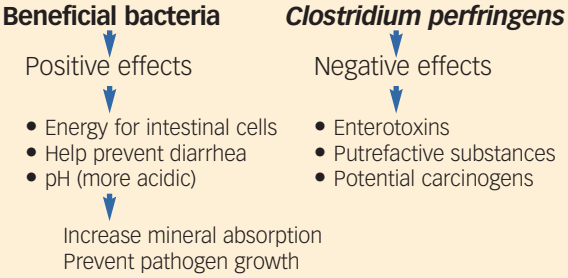
DIET

Dietary therapy is important in managing gastrointestinal disorders in the diabetic cat.[1] The presence of food in the gastrointestinal tract provides nutrients, increases mesenteric blood flow, and stimulates the release of digestive enzymes and hormones.[1] During acute diarrhea episodes in nondiabetic patients, complete bowel rest is advocated;[2] however, this is not possible in diabetic cats receiving twice-daily insulin injections.

Highly digestible, low-fiber diets (*e.g.*, Purina Veterinary Diets EN) are recommended for cats with gastrointestinal diseases, including inflammatory bowel disease not related to food allergy.[3,4] Such diets facilitate nutrient absorption in the proximal small bowel and reduce the antigenicity of bowel contents.[3] Carbohydrate malassimilation secondary to exocrine pancreatic insufficiency in diabetic cats can result in osmotic diarrhea, intestinal gaseousness, bacterial overgrowth, and other adverse effects.[3] Therefore, moderate restriction of dietary carbohydrates also may be beneficial for cats with gastrointestinal disease.[4] For cats with inflammatory bowel disease, diets with a modified (reduced) omega-6:omega-3 fatty acid ratio has been suggested to reduce gastrointestinal inflammation.[3-5] The cytokines produced from omega-3 fatty acids are less inflammatory than those produced from omega-6 fatty acids.[6]

A low-carbohydrate, high-protein diet that is similar to a cat's natural diet (*e.g.*, mice) may ameliorate some of the abnormalities associated with diabetes mellitus and concurrent gastrointestinal disease. A study examining clinical cases of diabetes mellitus in cats fed a high-protein, low-carbohydrate food (Purina Veterinary Diets DM) showed that insulin dosage could be decreased by 50% and that 25% to 30% of cats could discontinue insulin altogether. There was also a significant reduction in concurrent diarrhea among study participants.[7]

Probiotics: Inside the large intestine



ANCILLARY MEDICATIONS

Probiotics

Probiotics (*e.g.*, Purina Veterinary Diets FortiFlora) are live microorganisms that, when ingested, have a beneficial effect on intestinal function by promoting improved intestinal microbial balance. The probiotic in FortiFlora is *Enterococcus faecium* strain SF68. The beneficial bacteria help to nourish the intestinal cells and protect against colonization by pathogenic bacteria, which can cause diarrhea (see *Probiotics: Inside the large intestine*). Probiotics are considered to be most beneficial for diarrhea caused by microflora imbalance resulting from stress, antibiotics, diet change, dietary indiscretion, and acute enteritis. In general, the longer the pet has had diarrhea, the longer it will take for probiotics to affect intestinal health. Animals with acute diarrhea will respond much more quickly than animals with a chronic problem. When used to prevent antibiotic-related diarrhea, it is best to begin feeding probiotics before treatment to help build the maximum level of good bacteria in the intestine and then to continue them after the antibiotics have been stopped. To maximize efficacy, probiotics should be given with a meal once a day but at a different time of day than the antibiotics. For acute cases, two weeks of probiotic therapy may be sufficient; however, most chronic cases will require at least 30 days.

Cobalamin

Older cats, particularly those more than 10 years old, are more likely to be vitamin B_{12} (cobalamin) deficient.[8] Diabetic cats with concurrent gastrointestinal

disease, particularly pancreatic insufficiency, may suffer from cobalamin deficiency. Cobalamin is assimilated via binding to intrinsic factor (from the pancreas) and subsequent absorption in the ileum; therefore, cats with exocrine pancreatic insufficiency, small intestinal bacterial overgrowth, and ileal disease should be screened for cobalamin deficiency. Cobalamin is a cofactor for enzymes involved in transmethylation, DNA synthesis, and cellular turnover. Cobalamin deficiency is manifested as an unthrifty appearance; anorexia; lack of weight gain; anemia; and, in the case of diabetic cats, poor diabetic regulation. It is recommended that cats with significant gastrointestinal signs have serum cobalamin levels measured by a reputable laboratory. Infiltrative disease of the gastrointestinal tract may cause a decrease in cobalamin absorption from the ileum; therefore, oral supplementation is usually not sufficient to overcome this vitamin deficiency. Injectable B_{12} supplementation with 250 µg/cat subcutaneously every week for six weeks, then one dose every two weeks, and then once monthly is recommended.

Antibiotics

Managing concurrent gastrointestinal diseases may require the use of antibiotics. Since many gastrointestinal bacteria are anaerobic, antibiotics that have an anaerobic, gram-positive spectrum should be used, such as clindamycin, metronidazole, penicillins, cephalosporins, chloramphenicol, and tylosin.

Steroids

Diabetic cats with concurrent inflammatory bowel disease, pancreatitis, or cholangiohepatitis may benefit from corticosteroid administration. Short-acting, oral medications, such as medrol or prednisolone, should be used rather than repositol steroids, such as methylprednisolone acetate and triamcinolone. This is because repositol steroids, unlike oral steroids, do not undergo partial inactivation in the liver (the "first pass effect") and, therefore, contribute significantly to peripheral insulin resistance. In my experience, there is little to no effect on blood glucose management when using oral steroids. It is unclear if certain cats can convert prednisone to the active form, prednisolone; therefore, either prednisolone or methylprednisolone are recommended to obtain optimal efficacy. A daily oral dose of prednisolone (5 mg) or methylprednisolone (4 mg) is recommended. A course of 14 days is used in acute flare-ups, or a gradual reduction in daily dose to 2.5 mg or 2 mg, respectively, can be used to manage chronic cases of inflammatory bowel disease.

CONCLUSION

Diabetic cats that remain on insulin as a result of irreversible pancreatic damage from the diabetic state may exhibit gastrointestinal signs that are difficult to manage. Proper use of a diet that is low in carbohydrates and high in protein and omega-3 fatty acids may ameliorate some of the gastrointestinal signs of concurrent conditions, such as inflammatory bowel disease or pancreatitis. In addition, ancillary medications including cobalamin (vitamin B_{12}) supplementation, probiotics, antibiotics, and corticosteroids may improve both the gastrointestinal signs and the diabetic regulation.

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Canine pancreatitis: A RATIONAL APPROACH TO DIAGNOSIS AND THERAPY

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The incidence of exocrine pancreatic disorders in dogs is quite high. In a large retrospective study of necropsy findings, 1.5% of 9,342 canine pancreata showed significant pathologic lesions.[1] Approximately 50% of all canine patients with exocrine pancreatic disorders have pancreatitis, and approximately two-thirds of dogs with pancreatitis have acute disease.

According to the current classification system of human pancreatitis, acute pancreatitis is an inflammatory condition of the pancreas that is completely reversible after removal of the inciting cause.[2] Chronic pancreatitis is characterized by irreversible histopathologic changes (*i.e.*, fibrosis, atrophy, or both) of exocrine pancreatic tissue. Both forms can be mild or severe. Mild forms of pancreatitis are associated with no or little pancreatic necrosis and systemic complications, and the patient often recuperates. In contrast, severe forms of pancreatitis are associated with extensive pancreatic necrosis and multiple organ involvement, and the patient's prognosis is often poor.

ETIOLOGY AND PATHOGENESIS

Several diseases and risk factors have been associated with pancreatitis.[3] Hyperlipidemia and dietary indiscretion have been implicated in causing canine pancreatitis, but experimental evidence supporting this connection is sparse. Trauma following road or traffic accidents has been reported as a cause of pancreatitis. Surgical trauma can cause pancreatitis, but many people who undergo surgery on organs distant from the pancreas also show an increased risk for pancreatitis, suggesting that hypoperfusion of the exocrine pancreas during anesthesia may be a bigger concern than surgically handling the organ itself. Infectious agents, such as *Toxoplasma gondii* or hepatic fluke infestation, have been shown to cause rare cases of pancreatitis in cats but not in dogs.[4] Many pharmaceutical compounds (*e.g.*, L-asparaginase, azathioprine, estrogen, furosemide, potassium bromide, salicylates, sulfonamides, tetracyclines, thiazide diuretics, vinca alkaloids) have been implicated as a cause of pancreatitis in people and dogs.[5] Finally, more than 90% of all cases of canine pancreatitis are idiopathic.

According to a generally accepted pathogenic model, pancreatic

Canine pancreatitis:
A RATIONAL APPROACH

acinar cells ultimately respond in a common fashion to a variety of harmful stimuli.[6] Recent data suggest that the exocrine pancreas responds to several different noxious stimuli with a decrease in pancreatic enzyme secretion, followed by the formation of giant cytoplasmic vacuoles in acinar cells. Biochemical studies have shown that these vacuoles, which are only visible by electron microscopy, are formed when zymogen granules and lysosomes (which are normally strictly segregated) co-localize. The ensuing decrease in pH and/or the presence of lysosomal enzymes, such as cathepsin B, lead to premature trypsinogen activation. Trypsin, in turn, activates other zymogens, leading to local effects such as inflammation, pancreatic edema and hemorrhage, pancreatic necrosis, and parapancreatic fat necrosis. These local effects are associated with clinical signs such as vomiting and abdominal pain.

While vomiting and cranial abdominal pain are not specific to pancreatitis, they are key clinical signs in dogs with pancreatitis, and a dog presenting with both of these signs should be carefully evaluated for the presence of pancreatitis.

Until recently, systemic signs commonly seen in patients with pancreatitis were believed to be the direct result of circulating pancreatic enzymes, similar to local effects. While there is little doubt that some of these systemic effects, such as lipodystrophy, are caused by circulating pancreatic enzymes, recent data suggest that other systemic sequelae are due to inflammatory mediators that are released in response to pancreatic inflammation. A systemic inflammatory response, which consists of neutrophil release; leukocyte chemotaxis; degranulation of mast cells, basophils, and eosinophils; and platelet aggregation, occurs commonly in patients with severe forms of pancreatitis.

More recently, cytokines are believed to play a more important role in the progression of pancreatitis and the development of systemic effects.[7]

CLINICAL PICTURE

Clinical signs in dogs with pancreatitis depend on the severity of the disease. Mild cases may remain subclinical. According to data from a study of 70 dogs with fatal pancreatitis, more severe cases may present with anorexia (91%), vomiting (90%), weakness (79%), abdominal pain (58%), dehydration (46%), or diarrhea (33%).[8]

Clinical signs in pancreatitis patients stem from local pancreatic inflammation or systemic effects. Local effects may include inflammation, hemorrhage, acinar cell necrosis, or peripancreatic fat necrosis. Systemic effects may include inflammatory changes, vasodilatation (leading to hypotension and sometimes acute renal failure), pulmonary edema (leading to respiratory failure), disseminated intravascular coagulation, lipodystrophy (also known as pancreatitis-associated panniculitis or Weber-Christian syndrome), central neurologic deficits (such as disorientation, which is sometimes referred to as pancreatic encephalopathy), renal failure, or multi-organ failure.

DIAGNOSTIC TESTS

A ***complete blood count*** (CBC) and ***serum chemistry profile*** often show mild and nonspecific changes.[8] More severe changes can be observed in patients with severe forms of pancreatitis.

Serum amylase and ***lipase*** activities have a limited clinical utility for diagnosing canine pancreatitis. The specificity of both of these parameters is only about 50%, even when stringent criteria are applied.[9] Thus, serum amylase and lipase activities should only be used if they can be performed in-house and only until more definitive diagnostic tests can be performed.

In some patients, ***abdominal radiography*** will show a decreased contrast in the cranial abdomen and displacement of abdominal organs. However, these changes are rather subjective, and abdominal radiography is nonspecific for canine pancreatitis.

In contrast, ***abdominal ultrasound*** is quite useful for diagnosing canine pancreatitis. The sensitivity of abdominal ultrasonography is 68% or less in dogs.[8] However, this number is largely operator-dependant. Changes identified through an abdominal ultrasound can include pancreatic swelling, hypoechogenicity of the pancreas (in cases of pancreatic necrosis), hyperechogenicity of the peripancreatic area (in cases of peripancreatic fat necrosis), hyperechogenicity of the pancreas (in rare cases of pancreatic

fibrosis), fluid accumulation around the pancreas, a mass effect in the area of the pancreas, a dilated pancreatic duct, or an enlarged duodenal papilla.

Abdominal computed tomography is a routine procedure in people with suspected pancreatitis but appears to be insensitive for diagnosing pancreatitis in dogs.

Trypsin-like immunoreactivity (TLI) is specific for exocrine pancreatic function, and serum canine TLI concentration remains the diagnostic test of choice for the diagnosis of EPI in dogs. However, the sensitivity of serum TLI concentration for pancreatitis in dogs is only about 30% to 60%, making it a suboptimal diagnostic test for pancreatitis.

An assay for measuring canine ***pancreatic lipase immunoreactivity*** (cPLI) has been developed and validated. Many different cell types in the body synthesize and secrete lipases. In contrast to catalytic assays, using an immunoassay allows the specific measurement of lipase originating from the exocrine pancreas. During pancreatitis, pancreatic acinar cells leak pancreatic enzymes and zymogens, and serum cPLI concentration is increased.

Recently, a new commercial assay, Spec cPL™ (IDEXX Laboratories), was introduced. Spec cPL is more robust than the original in-house assay developed at the Gastrointestinal Laboratory at Texas A&M University and has now replaced the original cPLI assay worldwide. Spec cPL concentration shows remarkable correlation with cPLI concentration, and all data presented for the cPLI assay can be directly applied to the new Spec cPL assay.

Traditionally, a ***pancreatic biopsy*** has been viewed as the most definitive diagnostic tool for pancreatitis. Pancreatic biopsies can be collected during abdominal exploratory surgery or by laparoscopy. In many cases, the presence of pancreatitis is easily diagnosed by gross appearance of the pancreas. However, the absence of pancreatitis can be difficult to prove. In a recent study, histopathologic findings in dogs diagnosed with pancreatitis were evaluated.[10] Pancreata were sectioned every 2 cm. In approximately 50% of all dogs with pancreatitis and in two-thirds of dogs with chronic pancreatitis, evidence of pancreatic inflammation was found in less than 25% of all sections. Thus, even if multiple biopsies are collected, pancreatic inflammation, especially in chronic cases, may easily be missed. This would also suggest that laparoscopy is an inferior method for collecting pancreatic biopsies because it is more difficult to evaluate the entire organ. It should also be noted that while a pancreatic biopsy is not associated with excessive complications, many patients with severe pancreatitis are a poor anesthetic risk.

THERAPY

Veterinarians should address and treat the inciting cause and provide supportive care. Exposure to unnecessary drugs, especially those implicated in causing pancreatitis in dogs or other species, should be avoided.

Fluid therapy. Aggressive fluid therapy is the mainstay of therapy. Fluid, electrolyte, and acid-base imbalances need to be assessed and corrected promptly.

Alimentation. The traditional recommendation for any patient with pancreatitis is to give nothing per os (NPO) for three to four days. This recommendation is justified in patients that vomit, but there is little evidence to substantiate this strategy in patients that do not. In fact, early feeding is considered beneficial in people with severe acute pancreatitis.[11] Preferred routes of alimentation in patients that are kept NPO are a jejunostomy tube or total parenteral nutrition. However, these strategies are impractical in many cases, and a gastrostomy tube, esophagostomy tube, or nasogastric tube are acceptable alternatives if the patient does not vomit. However, vomiting dogs should be held NPO for three to four days. After this time, water may be slowly reintroduced, followed by small amounts of a carbohydrate-rich, low-fat diet.

Analgesia. Abdominal pain is commonly recognized in dogs with pancreatitis. Even if not recognized, veterinarians should assume that abdominal pain is present and administer analgesic drugs. Meperidine, butorphanol tartrate, or morphine can be used parenterally. Other alternatives include a fentanyl patch or intra-abdominal lidocaine administration.

Plasma. Studies in dogs suggest that death ensues rapidly when alpha-2-macroglobulin, one of the scavenger proteins for activated proteases in serum, is depleted. Fresh frozen plasma and fresh whole

Why is cPLI concentration the most sensitive and specific diagnostic test for canine pancreatitis?

In one study, canine pancreatic lipase immunoreactivity (cPLI) concentrations were measured in a group of dogs with exocrine pancreatic insufficiency.[1] The median serum cPLI concentration was significantly lower compared with healthy dogs. In addition, serum cPLI concentration was non-detectable in most of the dogs with exocrine pancreatic insufficiency, and minimal serum cPLI concentrations were observed in the rest of the dogs, indicating that serum cPLI concentration originates from the exocrine pancreas and is specific for exocrine pancreatic function.

In another study, serum cPLI concentrations were evaluated in dogs with experimentally induced chronic renal failure.[2] While serum cPLI was significantly higher in those dogs than in healthy dogs, most affected dogs had serum cPLI concentrations within the reference range, and none of the affected dogs had a serum cPLI concentration that was above the currently recommended cut-off value for the diagnosis of pancreatitis. This study suggests that serum cPLI concentration can be used as a diagnostic test for pancreatitis even in dogs with renal failure. Also, long-term oral administration of prednisone did not have any effect on serum cPLI concentration.[3]

Finally, another study compared the sensitivity of different minimally invasive diagnostic tests in dogs with proven pancreatitis. The sensitivity of serum TLI concentration was less than 35%, and the sensitivity of serum lipase activity was less than 55%. In contrast, the sensitivity of serum cPLI concentration for pancreatitis was more than 80%.[4] Thus, serum cPLI concentration is the most sensitive and specific diagnostic test for canine pancreatitis currently available.

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blood contain not only alpha-2-macroglobulin but albumin, which should have many beneficial effects in patients with severe pancreatitis. However, clinical trials could not identify any benefits of plasma administration in people with acute pancreatitis.[12] Regardless, the author believes that fresh frozen plasma administration is clinically useful in dogs with severe forms of pancreatitis.

Antibiotic therapy. In contrast to people, infectious complications (*e.g.*, infected necrosis) are rare in dogs with pancreatitis. Therefore, the use of antibiotics should be limited to cases in which veterinarians identify an infectious complication or heavily suspect one.

Anti-inflammatory agents. There are no data on using anti-inflammatory agents (*e.g.*, corticosteroids or nonsteroidal anti-inflammatory drugs) in dogs with severe pancreatitis, but no benefit has been found in people. In dogs with severe pancreatitis, corticosteroids should only be used when secondary cardiovascular shock occurs. However, corticosteroids do not appear to be harmful in dogs with inflammatory bowel disease and concurrent mild chronic pancreatitis, and such patients may require corticosteroid administration.

Other therapeutic strategies. All of the following treatment modalities have been evaluated in people with pancreatitis: trypsin-inhibitors (*e.g.*, aprotinin), platelet activating factor inhibitors, dopamine, antacids, antisecretory agents (*e.g.*, anticholinergics, somatostatin), antioxidants (*e.g.*, selenium), and surgical intervention. With the exception of

platelet activating factor inhibitors and selenium, none of these have shown any beneficial effect. In an uncontrolled study, selenium was shown to decrease mortality in dogs with pancreatitis, but further efficacy evaluations are necessary before recommending its use.[13]

MILD CHRONIC PANCREATITIS

Many dogs have mild forms of chronic pancreatitis. These patients often have concurrent conditions, most notably inflammatory bowel disease. Very little is known about appropriate therapy for these animals, and management is often limited to evaluating and treating the inflammatory bowel disease and carefully monitoring the pancreatitis. Practitioners should also evaluate serum calcium and triglyceride concentrations to identify risk factors (*e.g.*, hypercalcemia or hypertriglyceridemia) that could be addressed therapeutically. They should also recommend a low-fat diet.

Using corticosteroids in patients with mild chronic pancreatitis is controversial. In people with pancreatitis, a subset is being diagnosed with immune-mediated pancreatitis. These patients respond well to corticosteroid administration. Many dogs with chronic pancreatitis show lymphocytic-plasmacytic infiltration of the exocrine pancreas, similar to what is observed in people with immune-mediated pancreatitis. Thus, some dogs with mild chronic pancreatitis may also respond favorably to corticosteroid administration. Just like people with chronic pancreatitis, dogs with mild chronic pancreatitis are at risk for developing episodes of severe pancreatitis at any time or exocrine pancreatic insufficiency later in life.

PROGNOSIS

The prognosis for dogs with pancreatitis is directly related to the severity of the disease, extent of pancreatic necrosis, occurrence of systemic and pancreatic complications, duration of the condition, and presence of concurrent disease.

CONCLUSION

Pancreatitis occurs frequently in dogs, and cases range in severity from subclinical to peracute. Diagnosing pancreatitis remains challenging, especially in mild cases, but a combination of the serum Spec cPL concentration measurement and abdominal ultrasound is very useful to determine a diagnosis of canine pancreatitis. Treatment of pancreatitis should be aimed at treating the inciting cause (if identified) and providing supportive care (*e.g.*, analgesics, antiemetics, fluid therapy, nutritional support, and maintenance of electrolyte balance).

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