CHAPTER

35

Concurrent Disease Management

OUTLINE

HYPERTHYROIDISM AND CHRONIC KIDNEY DISEASE

Sarah Caney

The most common concurrent illness seen in association with hyperthyroidism is chronic kidney disease (CKD). Both illnesses are common in the older cat and the presence of CKD not only affects diagnosis of hyperthyroidism but also treatment and prognosis. Accurate assessment of patients is required to identify the concurrent problem and any associated complications that may require additional treatment. A more cautious approach to treatment is required to prevent destabilization of a vulnerable patient. With care, it is usually possible to manage both conditions successfully and provide the patient with a good quality and length of life.

Authors of a recent study reported that 14% of hyperthyroid cats had preexisting CKD on first assessment of thyroid disease.[167] Whether there is a causal relationship between hyperthyroidism and CKD or whether both conditions simply occur in concert is not known because they are both common conditions in the older individual. The relationship between these two conditions is complex. It has been postulated that hyperthyroidism causes damage to the kidneys, which may contribute toward long-term development of CKD through several mechanisms. These include tubulointerstitial damage, ultimately fibrosis, and chronic interstitial nephritis caused by an increase in angiotensin II. In addition, systemic hypertension present in a proportion of hyperthyroid cats may contribute to renal damage through microinfarction and subsequent fibrosis. This last effect is recognized in the micropuncture studies on the remnant kidney cat model.[157] Whether this occurs in hypertensive cats with naturally occurring CKD is unknown. However, it is also speculated that hyperthyroidism, in fact, merely masks a preexisting decline in renal function by increasing renal blood flow and hence glomerular filtration rate (GFR).

DIAGNOSTIC CHALLENGES

Evaluation of blood and urine samples is important in the assessment of both hyperthyroid and CKD patients. It not only is valuable in diagnosing these conditions but also in assessing severity and looking for the presence of additional illnesses. Unfortunately, in the case of cats with concurrent hyperthyroidism and CKD, interpretation of laboratory tests becomes especially challenging.

The presence of CKD can make diagnosis of hyperthyroidism problematic because of suppression of thyroid hormones—the so-called sick euthyroid syndrome. Therefore in cats with clinical signs compatible with hyperthyroidism, a normal total thyroxine (total T_4) should not be taken as evidence that the cat does not have this condition. Cats having both creatinine and total T_4 concentrations in the upper normal reference range are likely to have both hyperthyroidism and CKD.[238]

If a normal T_4 result is obtained in a cat suspected of being hyperthyroid, there are several options for further diagnosis. Repeating the same test on another occasion (for example, a few weeks later) can be helpful in those cases where the hyperthyroidism is mild, since fluctuation in levels of thyroxine can result in the total T_4 being intermittently within the reference range. Measurement of free T_4 by equilibrium dialysis is another option. This test is more sensitive in identifying hyperthyroid cats but carries a slightly higher risk of false-positive results (i.e., over diagnosing hyperthyroidism) so is not generally recommended as a screening test for hyperthyroidism.[182] A total T_4 greater than 30 nmol/L (greater than 2.33 μg/dL) in addition to a high free T_4 is supportive of a diagnosis of hyperthyroidism; conversely, if the total T_4 is less than 30 nmol/L (less than 2.33 μg/dL) the cat is extremely unlikely to have hyperthyroidism.[238] Where available, analysis of endogenous thyroid-stimulating hormone (TSH) can be helpful, with hyperthyroid cats having low levels.[238] Thyroid scintigraphy, triiodothyronine (T_3) suppression, and thyrotropin-releasing hormone (TRH) stimulation tests[226] can also be helpful in discriminating hyperthyroid from sick euthyroid patients. Unfortunately, all of these tests are affected by severity of concurrent disease, which can make interpretation of results difficult.

The presence of CKD can affect serum biochemistry and hematology results. Laboratory consequences of hyperthyroidism, such as erythrocytosis, occasionally seen in hyperthyroid cats, may be masked by anemia associated with CKD.

Identifying the presence and quantifying the severity of renal disease in a hyperthyroid cat is difficult. Assessment of kidney function currently depends upon measurement of blood urea and creatinine levels in association with urine specific gravity. Azotemia (elevated blood urea and/or blood creatinine) along with a reduced urine specific gravity are used to diagnose reduced renal function. However, concentrations of urea and creatinine can be affected by hyperthyroidism, and this complicates interpretation of serum chemistry results. Urea tends to be high in hyperthyroid cats as a consequence of polyphagia (and hence increased protein intake), and this may falsely increase the concern that a hyperthyroid cat has CKD. Conversely, creatinine concentrations tend to be misleadingly low, because hyperthyroid cats are thin and have very little muscle mass (creatinine being derived from muscle turnover). The increased GFR present in hyperthyroid cats also tends to reduce blood levels of both urea and creatinine.

Assessment of urine specific gravity is usually helpful to define renal function, but this too can be affected by hyperthyroidism. A healthy urine specific gravity (USG) is generally considered to be greater than 1.040, with concentrations less than 1.035 taken as one of the indications of kidney disease. However, in hyperthyroid cats, the ability to produce concentrated urine is compromised, and a USG less than this figure can be obtained from cats that have healthy kidneys. Additionally, this healthy value varies with the type of diet fed. Cats fed strictly dry food should concentrate urine to greater than 1.045, whereas a USG of greater than 1.025 may be appropriate in cats fed exclusively canned/moist food.[45]

Mild proteinuria is a common finding in hyperthyroid cats.[222] It is thought that the proteinuria may be present as a consequence of glomerular hypertension and hyperfiltration that is known to occur in the hyperthyroid state. The prognostic significance of proteinuria in hyperthyroidism is currently unknown, but it does tend to resolve with treatment, even in cats that develop azotemia.[222,224]

Both hyperthyroidism and CKD are conditions associated with a higher incidence of urinary tract infections. For example, one study showed that 12% of hyperthyroid cats suffered from urinary tract infections.[158] Unfortunately, most of these cats suffer from clinically silent urinary infections and may only show vague clinical signs, such as weight loss and lethargy. It is important to be suspicious of infection and culture the urine to identify and treat any of these additional problems, because it will benefit the cat's current and long-term prognosis.

TREATING CATS WITH CONCURRENT HYPERTHYROIDISM AND CHRONIC KIDNEY DISEASE

All treatments for hyperthyroidism have the potential to worsen kidney function.[58] This is because the hyperthyroid condition increases renal blood flow and GFR. When the hyperthyroidism is treated, the increased cardiac output and renal blood flow to the kidneys decreases. This results in a decrease in GFR by up to 50% of the pretreatment level.[11,16,83] For many hyperthyroid cats, this return to normality is not associated with kidney problems. However, in a proportion of patients, this reduction in blood flow has the potential to unmask kidney disease that was not previously recognized, allowing the preexisting kidney disease to manifest itself clinically. In those cats in which renal disease has been documented before treatment is started, treatment has the potential to worsen renal function and may precipitate a crisis. The reported frequency of this complication has varied in publications. In one report, one third of patients developed this complication following treatment with radioiodine, while other reports have found even higher numbers of cats experiencing a crisis after treatment.[58,212] Affected cats become azotemic and may start to show clinical signs of renal disease. Significant decreases in renal function are generally evident by 4 weeks posttreatment, after which time GFR stabilizes with very little deterioration, depending on the degree or stage of renal disease.[16,233,234]

A number of studies have shown that it is not possible to predict accurately which patients will reveal CKD following treatment of hyperthyroidism. These studies have evaluated pretreatment laboratory variables, such as serum biochemistry, USG, proteinuria, and hematology.[16,192,222,234] In general, no significant differences have been seen when comparing the pretreatment parameters in cats that did develop a posttreatment renal azotemia with those that did not. Although USG is reduced in cats with CKD, it also can be reduced as a consequence of hyperthyroidism, so analysis of this parameter alone is not sufficient to be helpful. Equally, although a pretreatment USG of greater than 1.035 is often reassuring, it cannot be viewed as a guarantee that the cat will not develop a posttreatment renal azotemia.[192] The fact that some cats with primary renal azotemia remain able to concentrate urine to 1.045 or greater complicates the interpretation further.[174]

GFR is reported to be of some value in predicting posttreatment renal azotemia.[2,234] One study reported some value in using a combination of pretreatment GFR, USG, and total T_4 in predicting which patients developed a posttreatment renal azotemia.[234] In the same study, there was a significant difference in pretreatment GFR and USG in those cats that eventually developed posttreatment renal azotemia. Unfortunately, assessment of GFR is not readily available in clinical practice, limiting its usefulness. Iohexol clearance has been evaluated and could be a clinically feasible tool; however, it has not become part of mainstream diagnostics.[11] The usefulness of other markers of renal function, such as the NAG index (urinary N-acetyl-beta-D-glucosaminidase to urinary creatinine ratio) and urinary retinol binding protein, are still being evaluated.[144,232]

For these reasons, most clinicians prefer to treat all hyperthyroid cats with medical management in the first instance. The main advantage of this approach is that it is reversible; in other words, if renal function deteriorates, the treatment for hyperthyroidism can be reduced or discontinued to help stabilize the patient. Medical treatment of hyperthyroidism induces euthyroidism more gradually than surgical thyroidectomy or radioiodine therapy, both of which may result in an acute destabilization of a patient. In cats in which renal function remains stable on medical treatment, permanent treatment of the hyperthyroidism can be considered with a greater degree of confidence. Although no definite guidelines exist, it is probably advisable to monitor

patients on medical treatment for at least a few months, possibly as long as 6 months, before making a decision to elect for more permanent, curative treatments.

If a cat is known to have CKD before medical treatment for hyperthyroidism is started, it is probably advisable to start treatment with a lower dose of medication initially while monitoring the renal values closely. For example, if using methimazole, a starting dose of 1.25 to 5 mg every 24 hours should be considered. If any problems are seen, then the methimazole dose can be lowered or the treatment may be discontinued. If, conversely, medication is not associated with renal or other adverse effects, the dose can be titrated to induce and maintain euthyroidism. Frequent and regular re-evaluations are essential to facilitate optimal management of both CKD and hyperthyroidism. The author recommends initial assessment of renal parameters at 3 and 6 weeks following the start of treatment.[39]

Ongoing management of patients with both CKD and hyperthyroidism requires attention to both conditions. International Renal Interest Society (IRIS) guidelines (http://www.iris-kidney.com) should be followed with respect to staging and management of CKD and any complications present as a result of this. Where possible, attempts should be made to induce and maintain euthyroidism as discussed above. In those patients where euthyroidism is associated with a clinical and biochemical worsening of renal disease, it may be necessary to titrate therapy to achieve the best balance possible. The individual priorities of each patient need to be considered to determine which therapy and approach is most appropriate. For example, in some patients, suboptimal control of the hyperthyroidism may be tolerated clinically, whereas euthyroidism may be associated with severe renal dysfunction and a clinical crisis. Success of treatment should be gauged on clinical response to treatment as well as assessment of laboratory parameters. Accurate assessment of body weight and body condition score is vital in addition to a thorough history, general clinical examination, and blood pressure measurement. Fortunately, in many cats, it is possible to achieve a balance between these two conditions and gain a good treatment outcome.

HYPERTHYROIDISM AND DIABETES MELLITUS

Margarethe Hoenig

PREVALENCE

Hyperthyroidism in cats was virtually unknown until the late 1970s and is now the most common endocrine disease of cats and one of the most common diseases in older cats. Diabetes mellitus (DM) is also a commonly encountered endocrine problem in older cats, and its prevalence also has increased dramatically in the last three decades because of a large increase in the prevalence of obesity. According to Joslin (writing in 1934),[128] in people, "the subject of hyperthyroidism and diabetes, as a combination of diseases, is such a small one that it permits but little to be said about," even though diabetes not infrequently co-exists with hypothyroidism and hyperthyroidism in human patients. It is not known how frequently the two diseases co-exist in cats, but anecdotally, it is well known that they can occur concomitantly. There are, however, no epidemiologic or pathophysiologic data linking hyperthyroidism with diabetes, nor is an increase in fasting blood glucose a common feature of the hyperthyroid cat.

PATIENT SIGNALMENT AND RISK FACTORS

Although the increase in both diseases has occurred during the same time span, that is, the last 3 decades, it does not appear that identical factors are involved in the pathogenesis except for the fact that hyperthyroidism and DM occur primarily in older cats, and most patients are more than 10 years old. Hyperthyroidism and DM in young cats are extremely rare, with the exception of DM in Burmese cats in Australia. Other risk factors for DM are body condition (obesity), sex, and reproductive status.[205] At highest risk would be an old, obese, neutered male cat. A genetic predisposition appears to occur in Australian Burmese cats. The marked increase in DM in cats can be traced to the increase in feline obesity.

Several investigators from different continents have evaluated the risk factors for hyperthyroidism and have presented very similar results despite their geographic differences.[64,173,237] As stated, older domestic short- and long-haired cats were more likely to develop the disease than young or purebred cats. The risk increased with increasing age. There was no difference in the risk for males versus females in one study, whereas female cats were identified at higher risk in the others. Hyperthyroid cats were more likely to have used a litter box, to be fed wet cat food from a pop-top can, or were fed all categories of table food, including high-fat dairy products. The plasticizer compounds bisphenol A and phthalates have been suspected, without proof, as a causative agent for obesity and diabetes in man and for hyperthyroidism in cats, but no linkage has been ascertained to date. Environmental factors appear to play an important role, because hyperthyroid cats were more likely to have been exposed to smokers in their environment and to household insecticide treatments. Other risk factors include sleeping on the floor, exposure to organic fertilizers, and dental disease. Interestingly, hyperthyroidism

was less likely in multicat households compared with single-cat households.

CLINICAL SIGNS

It is impossible to clearly distinguish hyperthyroidism from DM based on the clinical presentation. The most frequently seen clinical signs for hyperthyroidism and DM are the same, are also similar to other chronic diseases of cats, and will worsen over time. As a result, the early recognition of hyperthyroidism in a diabetic cat and vice versa is difficult because of the shared clinical signs:

- Weight loss
- Excess appetite or inappetence
- Polyuria and polydipsia

Less predictably, both conditions may present with muscle weakness, vomiting, and diarrhea. In addition, cats with extreme hyperthyroidism may show agitation. The diabetic cat with acromegaly may gain, rather than lose weight.[15]

PATHOPHYSIOLOGY

Hyperthyroidism and diabetes are both catabolic states. Hyperthyroidism is caused by excessive secretion of thyroid hormones (triiodothyronine [T_3] and thyroxine [T_4]) by hyperplastic or adenomatous thyroid glands, rarely by malignant thyroid carcinomas.[106,181] Hyperthyroidism in cats is most similar to hyperthyroidism in people caused by toxic nodular goiter. Abnormalities of the G protein and 3′-5′-cyclic adenosine monophosphate (cAMP)-signaling pathway have been implicated in the pathogenesis in both species.[95,178] Although in people antibodies against islet antigens are found with autoimmune thyroid disease, there is no evidence that a similar connection exists in hyperthyroid cats. Autoimmune processes have not been shown to play a role in either disease, and islet antigens have not been detected in diabetic cats.[110]

Thyroid hormones (TH) affect many aspects of metabolism and energy homeostasis, and in general terms, can be viewed as antagonists to insulin. The metabolic alterations during thyrotoxicosis represent direct effects of TH on the expression of TH-responsive genes and are mediated by binding of T_3 to TH receptors in peripheral organs.[10,253] Thyrotoxic human patients exhibit insulin resistance, that is, the effectiveness of insulin in muscle, fat, and liver is hampered.[15,128,136,178,179] Because one of the main roles of insulin is the control of glucose homeostasis, increased insulin resistance is seen as a decrease in glucose tolerance. In a study comparing healthy with hyperthyroid cats, glucose clearance was decreased in hyperthyroid cats, and insulin secretion was increased during an intravenous glucose tolerance test.[105] This pattern is characteristic for peripheral insulin resistance, which causes decreased uptake of glucose into muscle and fat tissue. However, fasting blood glucose concentrations were still normal, suggesting that hepatic glucose output was still normal.

It is known that hyperthyroidism by itself causes increased hepatic glucose production and a dramatic increase in Krebs cycle flux.[59,131,137] One might therefore expect excess glucose production in thyrotoxicosis. However, we have shown in cats that pyruvate cycling flux, a futile cycle, is also stimulated by thyroid hormone, thereby negating an effect on gluconeogenesis.[136] It is conceivable that in hyperthyroid cats, gluconeogenesis is kept low, and fasting blood glucose is kept in the normal range through enhancement of this futile cycle. It has been shown in hyperthyroid rats that gluconeogenesis was only increased 20%, because pyruvate cycling decreased gluconeogenesis by more than two thirds compared with what would be seen were pyruvate cycling not operative, suggesting that pyruvate cycling plays a functional role in protecting against overproduction of glucose in liver.[126] Hyperglycemia is therefore not a feature of hyperthyroidism. Contrary to popular belief, there is no evidence that hyperthyroidism increases intestinal glucose absorption in cats, and data from other species are highly controversial.[165,189]

In contrast to the effect of hyperthyroidism on hepatic glucose regulation, the diabetic cat has lost the ability to regulate glucose output from the liver and shows high fasting blood glucose concentrations. Although it is possible that hyperthyroidism beneficially affects gluconeogenesis in diabetic cats to some degree, it does not overcome the detrimental effects of absolute or relative insulin deficiency that are seen with diabetes. It is certainly conceivable that hyperthyroidism long term could lead to diabetes, because it causes insulin resistance, and insulin resistance is a risk factor for diabetes, but this needs to be investigated in a well-controlled study. To date, there is no evidence for such a link. The deciding factor would be beta-cell mass. As long as a cat has a relatively large beta-cell mass, it will be able to withstand the insult of insulin resistance.

DIAGNOSIS

The diagnosis of hyperthyroidism may be more difficult in a diabetic cat than in a cat with hyperthyroidism alone, because of several confounding factors.

Serum Total Thyroxine (TT_4) Concentration

It has been well documented that nonthyroidal diseases suppress circulating TT_4 concentrations in cats. In fact,

diabetes mellitus has one of the most profound effects to reduce TT_4.[182] If TT_4 is normal in a diabetic cat suspected of hyperthyroidism, other tests are indicated, such as circulating free T_4 concentration by dialysis (FT_4D), nuclear scintigraphy, T_3 suppression test, or thyrotropin-releasing hormone (TRH) stimulation. However, normal, and occasionally high, TT_4 and high free T_4 has also been described in obese cats as well (see below). The functional tests (TRH stimulation, T_3 suppression, scintigraphy) have not been systematically studied in obesity, but none of these tests have shown high diagnostic specificity in cases of hyperthyroidism with concomitant nonthyroidal illness.[180,182,226]

Serum Free T_4 Concentration by Dialysis (FT_4D)

Free T_4 concentrations are high in hyperthyroidism and usually normal in cats with diabetes. When cats become obese, FT_4D increases for that animal because of increasing concentrations of non-esterified fatty acids that displace the hormone from its serum binding sites. However, at least in experimentally induced obesity, the FT_4D concentrations usually remain within the normal range.

Fructosamine

In unregulated diabetic cats, serum fructosamine concentrations are high, whereas in hyperthyroid cats, concentration of serum fructosamine may be low because of accelerated protein turnover.[191] Therefore fructosamine concentrations should not be used solely as an indicator of glycemic control in the diabetic cat with concurrent hyperthyroidism.

TREATMENT

If cats develop both diseases, in most instances one occurs before the other. In the case of the cat that is hyperthyroid first and develops diabetes later, the hyperthyroid condition usually has already been well controlled before diabetes occurs and the hyperthyroidism does not affect diabetes treatment.

If a well-controlled diabetic cat develops hyperthyroidism, the glucose control usually deteriorates and the insulin dose needs to be increased to avoid hyperglycemia. Once treatment for hyperthyroidism has begun and hyperthyroidism-induced insulin resistance is reduced, the insulin dose needs to be decreased to avoid hypoglycemia. Diabetes has not been shown to have any influence on the efficacy of drugs used for the treatment of hyperthyroidism, and no dose adjustment of those drugs is needed.

DIABETES MELLITUS AND OBESITY

Margarethe Hoenig

Obesity is the most common nutritional disorder, and diabetes mellitus (DM) is one of the most common endocrine diseases in cats. The prevalence for both has increased dramatically in the last 3 decades. Obesity is now thought to occur in about 40% and DM in about 0.5% to 1% of the cat population. Environmental factors, such as unrestricted food intake and reduced physical activity, are largely responsible for the modern epidemic of obesity. Obesity and DM are tightly linked to each other in cats, as they are in people. It is thought that feline obesity increases the risk to develop diabetes threefold to fivefold. Other risk factors for diabetes are gonadectomy and sex. Obese male neutered cats have the highest risk to develop the disease.[205]

DEFINITION OF DIABETES MELLITUS

Unlike in people, a diagnosis of DM in cats is usually only made when the animal exhibits obvious clinical signs of hyperglycemia. In people, an oral glucose tolerance test (OGTT) is a frequently used test to document diabetes but is rarely applied in pets. In asymptomatic people, a diagnosis of impaired glucose tolerance or diabetes is usually made based on fasting glucose concentrations and the response to a 75-g glucose load. Strict criteria have been established for the interpretation of the results to separate healthy people from people at risk of developing diabetes or already having diabetes. Oral glucose tolerance testing has recently been described in cats.[108] However, as in dogs, the OGTT in cats is associated with high variability of results and is not recommended as a routine clinical diagnostic test. The intravenous glucose tolerance test, although associated with less variability, is labor intensive and not suited for use in clinical practice. Therefore early recognition of cats at risk of developing diabetes is difficult, and no clear pattern of easily measurable parameters has emerged yet that would indicate development or progression of the disease process.

DEFINITION OF OBESITY

Obesity occurs when energy intake exceeds energy output. There are subjective as well as objective methods to measure increases in body mass. One of two (5- or 9-point scales) condition scoring systems are frequently used in practice.[142] Although subjective, they can be easily performed by one person. Longitudinal assessment (i.e., repeated over time) of animals should preferably be performed by the same person to decrease the

variability of results. A score of 3/5 or 5/9 indicates that the cat is well proportioned, that is, of normal weight, while a body condition score of 5/5 or 9/9 indicates that the cat is obese and has heavy deposits of fat. Values in between indicate the increase in fat deposits as the numbers rise. Girth circumference may be measured behind the last rib and is a good objective indicator of obesity. Similar to body condition scoring, it can also be performed by one person. Its results correlate very well with fat measurements using more sophisticated methods, such as dual-energy x-ray absorptiometry (DEXA).[109] Because normal girth values are not available for different cat breeds, at this time, this method should only be used to follow the body condition in a given individual animal over time. Plain radiographs may also be helpful in assessing condition by evaluating falciform and paralumbar fat deposits. Other objective methods, such as body mass index, DEXA scanning, or magnetic resonance imaging have also been performed in cats, but not usually in clinical practice. Because normal ranges for those techniques are not available for different breeds, these tests are also valuable only when performed over time in the same cat.

THE LINK BETWEEN OBESITY AND DIABETES

Obesity, in many regards, can be seen as a precursor state to diabetes in humans and cats. It is thought that obese cats develop a form of diabetes that is similar to type 2 diabetes in humans, a disease that is characterized by insulin resistance often caused by obesity, abnormal secretion of insulin and other hormones, and amyloid deposition in the islets of Langerhans. Although many of the pathophysiologic changes are similar in obese and diabetic people and cats, there are also some differences.

It is known that obese cats are insulin resistant. Insulin resistance is the condition in which normal amounts of insulin do not produce a normal insulin response from cells. Insulin resistance is usually measured with a method called the euglycemic hyperinsulinemic clamp. Simply explained, this is a technique in which a constant amount of insulin is infused. Glucose is also infused in the amount necessary to keep blood glucose concentrations in the euglycemic range. The more sensitive a cat is to the effect of insulin, the more glucose needs to be infused. It has been shown in cats that every kilogram in weight gain leads to a 30% loss in the sensitivity to insulin.[111,112] Insulin resistance is seen in muscle, fat, and liver in obese people. In obese cats, the response to insulin is tissue dependent, and even in long-term obese cats, insulin resistance is only seen in adipose and fat tissue. In muscle and fat, the following changes are seen with obesity-induced insulin resistance:

- The expression of the insulin-sensitive, high-Km (i.e., requires a large amount of glucose to achieve maximum reaction velocity) glucose transporter type 4 (GLUT4) is decreased.
- The expression of GLUT1, the insulin-insensitive low-Km (i.e., requires only a small amount of substrate to become saturated and reach maximum velocity) glucose transporter type 1, is unchanged.

This leads to a decrease in glucose clearance when cats are challenged with a high glucose load. These cats do not show a change in glycosylated hemoglobin, and baseline glucose concentrations remain normal even in the long-term obese cat.[20]

An interesting phenomenon, and one that explains the normal baseline blood glucose in obese cats, is the fact that the liver remains responsive to insulin. In a recent study, using nuclear magnetic resonance spectroscopy, we were able to show that insulin suppresses hepatic endogenous glucose production (EGP) by reducing glycogenolysis and gluconeogenesis in obese cats. These cats were hyperinsulinemic, indicated by approximately doubled baseline peripheral insulin concentrations and yet had no difference in glucose concentrations compared with lean cats. This suggests that hepatic autoregulation is intact in obese cats despite peripheral insulin resistance and impaired glucose clearance.[136] The decreased EGP in obese cats might be a compensatory mechanism to ensure normal fasting glucose concentration. It appears therefore that a loss of hepatic autoregulation is an important step in the pathogenesis of diabetes in cats.

Obesity and diabetes are characterized by quantitative and qualitative alterations of insulin secretion. Insulin normally is secreted from beta cells in a biphasic manner in response to high glucose during an intravenous glucose tolerance test. In the cat as in people, other fuels such as amino acids potentiate the secretion of insulin in the presence of glucose. Characteristic changes that are seen in obese cats are a marked increase in the second or maintenance phase of insulin release. The amount of insulin secreted during the second phase is primarily an indicator of glucose uptake into peripheral tissues. Because of the change in glucose transport and the delayed clearance of glucose in obese insulin resistant cats, insulin secretion is increased to overcome the resistance. Over time, the persistent oversecretion leads to a decrease in total insulin secretory capacity, and the animal becomes diabetic when insulin no longer leads to a normal response.[60,107] It is not known when in the course of the development of diabetes hepatic insulin resistance develops and when increased hepatic glucose output contributes to increasing glucose concentrations (known as glucose toxicity) even in the basal state, thereby worsening the demand on beta cells and

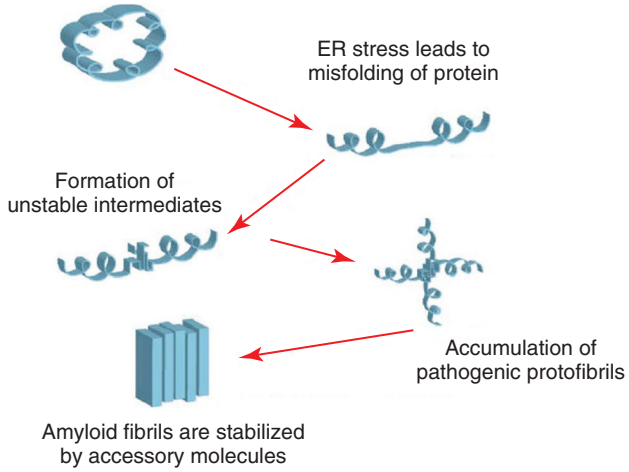

FIGURE 35-1 The effect of stress on endoplasmic reticulum amyloid formation. *(From Hayden MR, Tyagi SC, Kerklo MM, Nicolls MR: Type 2 Diabetes mellitus as a conformational disease,* JOP *6:287, 2005.)*

accelerating their exhaustion.[114] Eventually, beta cells will undergo apoptosis (programmed cell death).[60,195]

Islet amyloid is one of the characteristic features of feline diabetes and of human type 2 diabetes and is associated with a loss of beta cells. The precursor protein of islet amyloid is the hormone islet amyloid polypeptide (IAPP), which is co-localized in secretory granules of beta cells with insulin and is co-secreted with insulin.[129] It is not known why amyloid is formed in the diabetic cat. It is currently believed that the loss of beta cells associated with islet amyloidosis is actually caused by membrane permeable cytotoxic oligomers of IAPP rather than the final product, amyloid, and protective mechanisms in beta cells keeping IAPP in a soluble form must fail to allow these cytotoxic products to form.[93] Because the endoplasmic reticulum is responsible for the proper folding of proteins, including amyloid, it appears that any process that disturbs its function will lead to oligomer formation (Figure 35-1). There are no data about the occurrence of islet amyloid in obese cats compared with age-matched lean cats; however, we have shown that obese cats hypersecrete IAPP as well as insulin, which, long-term, might lead to disruption of regular secretory pathways.

Other hormones likely play a role in the progression from obesity to diabetes in cats (Table 35-1). Leptin is a hormone that is secreted from adipocytes. In lean animals, it leads to satiety and increases energy expenditure. It is known that obese cats have leptin resistance. Similar to the definition for insulin resistance, leptin resistance is the condition where normal amounts of leptin do not cause a normal response. Leptin concentrations are high in obese cats; yet, there is no decrease in food intake or increase in energy expenditure as would be expected in a cat that would respond normally.[6,112] The concentration of adiponectin, a hormone secreted from adipose tissue, which modulates glucose and lipid metabolism, is low in obese cats and correlates with insulin sensitivity.[112]

TABLE 35-1 Hormonal and Metabolic Changes in Obese Cats Compared with Lean Cats

Hormone	Concentration in Obese Cats	Effect
Adiponectin	Low	Decreased glucose and fat metabolism
Glucagon-like peptide-1	Low	Decreased hepatic glucose production Decreased gastric emptying Decreased satiety? Lower glucose-dependent insulin release
Insulin	High insulin resistance	Exhaustion of beta cells
Leptin	High leptin resistance	Decreased energy expenditure Decreased satiety?
Thyroid hormone	Higher but usually still within the normal range—thyroid hormone resistance?	Decreased energy expenditure

Thyroid hormone changes contribute to the metabolic alterations of obesity. The energy expenditure is lower in obese cats than lean cats but increases with administration of triiodothyronine (T_3), indicating that thyroid hormone is involved in the low heat production. It has also been shown that free T_4 has the strongest positive correlation with indices of obesity and increases with increases in body mass index, girth, leptin, and fatty acids. This suggests that obesity leads to a form of thyroid hormone resistance.[103,104]

Glucagon-like peptide 1 (GLP-1) has recently been examined in obese cats and was lower than in lean control cats.[108] Changes in GLP-1 concentrations have been associated with changes in glucose control in obese people and people with diabetes. It increases insulin secretion through activation of GLP-1 receptors on beta cells and increases the transcription of the proinsulin gene. It also inhibits glucagon secretion and regulates glucose homeostasis through decreasing glucose production by the liver, decreasing the rate of gastric emptying, and decreasing central effects on satiety.

Obese cats show a marked change in lipid metabolism. We found that obesity does have a significant effect on both plasma lipids and lipoprotein concentrations. Plasma triglycerides were found to be increased with obesity as was the very-low-density lipoprotein fraction (VLDL), the main carrier of triglycerides, whereas the

low-density lipoprotein fraction (LDL) was unchanged, and the high-density lipoprotein (HDL) fraction was decreased in long-term but not short-term obese cats compared with lean cats. Using nuclear magnetic resonance spectroscopy, we measured particle size and concentration within each of the lipoprotein fractions and found that obese cats have very similar changes to obese people who are at risk of developing atherosclerosis and cardiovascular disease. Those changes include more large VLDL particles, more medium- and small-sized LDL particles, and more small HDL particles.[127] Despite these changes, atherosclerosis and cardiovascular disease have not been described in obese cats, and only one study has suggested that there might be an increase in cardiovascular disease in diabetic cats; however, this needs to be confirmed in a well-controlled study. Not surprisingly, obese cats have a lower expression of peroxisome proliferator-activated receptors (PPARs), which are transcription factors that play a major role in the regulation of lipid, carbohydrate, and protein metabolism.[104]

Both high plasma glucose and fatty acid concentrations are involved in the mediation of oxidative stress through the generation of reactive oxygen species (primarily oxygen and nitrogen). Oxidative stress may play a role in the progression from obesity to diabetes, but so far this has not been studied in cats. Antibodies to islet antigens do not seem to play a role in the pathogenesis of diabetes in cats.[110] Interestingly, the metabolic sequelae of obesity are not at all, or only to a very limited degree, influenced by dietary components.

In conclusion, obesity is a major risk factor for the development of diabetes. It appears that loss of hepatic autoregulation may be the switch between obesity and diabetes in cats. Once the animal shows hyperglycemia, the toxic effects of glucose become evident as already shown in cats in 1948[60] and, in beta cells, lead to exaggerated apoptosis and further loss of beta-cell mass. It is important to know that the changes described above for obese cats can be reversed with a simple treatment, weight loss. This is one more reason to make sure feline obesity is recorded and treated before the path to diabetes becomes a one-way street.

DIABETES MELLITUS AND FELINE LOWER URINARY TRACT DISORDERS

Deborah S. Greco

Type 2 diabetes mellitus (DM) 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. Feline lower urinary tract disease (FLUTD) is a term that describes a constellation of disorders including feline idiopathic cystitis (FIC), which accounts for the majority of cases of FLUTD, urolithiasis, urethral plugs or other causes of obstruction, bacterial cystitis, and, rarely, neoplasia. The purpose of this chapter is to describe the etiology, prevalence, clinical signs, pathogenesis, diagnosis, and treatment of cats with concurrent DM and FLUTD.

ETIOLOGY AND PREVALENCE

Diabetes mellitus is one of the most common feline endocrine diseases. The etiology of type 2 DM is multifactorial, with obesity, genetics, diet, and islet amyloidosis involved in the development of this form of DM in humans and cats.[172,190,255] FLUTD occurs in approximately 1% to 3% of cats seen at general veterinary practices; the etiology is multifactorial, and a cat may be predisposed to the condition because of genetic, dietary, and environmental factors.[31,32,34,118,149]

Concurrent DM and FLUTD may result from two different scenarios. Cats with preexisting DM may experience signs of FLUTD, most often as a result of bacterial cystitis. Although bacterial infections are a rare (<1%) cause of FLUTD in nondiabetic cats, diabetic cats are predisposed to urinary tract infection (UTI) because of impaired local immunity and the presence of glucose (bacterial substrate) in the urine. If the cat has impaired renal function, decreased urine specific gravity (USG) may also contribute to a predisposition to UTI. On the other hand, cats presenting with signs of FLUTD or cats susceptible to repeated episodes of FIC may develop diabetes as a result of the stress of their disease (increased endogenous corticosteroids), inflammation associated with chronicity resulting in insulin resistance, or as a result of therapy for signs of FLUTD (if exogenous steroids have been used).

PATIENT SIGNALMENT AND RISK FACTORS

Risk factors for the development of diabetes mellitus in cats include increased body weight (>6.8 kg), older age (>10 years) and neutering.[176,185] Neutered males (NM) are 1.5 times more likely than females to develop diabetes mellitus. FLUTD is seen most commonly in cats that are young to middle aged, overweight, kept indoors, fed dry food *ad libitum* and live in a multianimal household.[31,32,34,38] Neutered cats are more susceptible, and the risk of urinary tract obstruction is greatest in males.[149] Concurrent FLUTD and DM is most likely to occur in obese middle-aged NM cats kept indoors.

CLINICAL SIGNS

Obesity combined with fasting or postprandial hyperglycemia may be the only clinical sign of early type 2 DM. Owners of diabetic cats may report gait abnormalities, weakness, inappropriate elimination (particularly if the litter box is large or placed in a remote location), and problems with jumping prior to the onset of polydipsia and polyuria.[85] Late signs of DM in cats include polydipsia, polyuria, anorexia, lethargy, and weight loss. The most common physical examination findings in cats suffering from DM are lethargy and depression (70%), dehydration (63%), unkempt hair coat (35%), and muscle wasting (47%).[85,185] Plantigrade rear limb stance resulting from diabetic neuropathy is observed in approximately 8% of diabetic cats.[185]

Cats with lower urinary tract disease can present with signs of dysuria, hematuria, pollakiuria, inappropriate urination, and/or urethral obstruction.[91,118] Nonobstructive cases are self-limiting, usually resolving within 5 to 10 days.

Clinical signs of concurrent diabetes mellitus and FLUTD may include polydipsia, polyuria, pollakiuria, dysuria, hematuria, and inappropriate elimination. In the author's experience, urethral obstruction is rare in a diabetic cat. However, there is considerable overlap in the clinical signs of DM and FLUTD; therefore careful assessment of the history and minimum database, including urine culture and serum fructosamine, may be necessary to make an accurate diagnosis.

PATHOPHYSIOLOGY

To summarize the current hypothesis of the pathogenesis of type 2 DM, peripheral insulin resistance (resulting from obesity, elevated plasma islet amyloid polypeptide [IAPP], or both) causes chronic stimulation of insulin production in the pancreatic beta cells.[190] Amylin is co-synthesized with insulin; therefore abnormal insulin secretion causes IAPP to accumulate in the beta cells.[172] The high local concentration of IAPP causes polymerization of IAPP to form insular amyloid. Eventually a vicious cycle of increased amyloid production and chronic hyperglycemia leads to beta-cell failure and apoptosis (programmed cell death).

Stress plays an important role in the pathogenesis of feline idiopathic cystitis. Recent studies indicate that FIC, the most common cause of FLUTD, may be caused by placing a "susceptible" cat into a "provocative" environment."[244,246,247,249] Activation of an abnormal pituitary-adrenal axis caused by genetic or epigenetic abnormalities, coupled with catecholamine excess caused by environmental stressors, leads to local bladder inflammation. Most cats with signs of FLUTD are obese, and the role of obesity in these diseases is poorly defined. Increased visceral fat causes inflammation[46,166] and predisposes to diseases, such as type 2 DM in both cats and humans. In fact, in the author's experience, many cats that eventually develop DM have had episodes of FLUTD prior to presentation with signs of diabetes.

DIAGNOSIS

Common clinicopathologic features of diabetes mellitus in cats include fasting hyperglycemia, hypercholesterolemia, increased liver enzymes (ALP, ALT), neutrophilic leukocytosis, possible proteinuria, variable urine specific gravity, bacteriuria, and glucosuria.[48] Many cats are susceptible to stress-induced hyperglycemia. In addition, renal glucosuria may be found in animals with renal tubular disease and with stress-induced hyperglycemia. Serum fructosamine evaluation may be beneficial in differentiating early or subclinical diabetes mellitus from stress-induced hyperglycemia in the cat. Serum fructosamine is formed by glycosylation of serum protein, such as albumin, and the concentration of fructosamine in serum is directly related to blood glucose concentration. One study of 17 normal cats showed that transient glucose administration (1 g/kg 50% glucose solution, intravenously) did not cause increased serum fructosamine concentrations.[153]

Cats with FLUTD typically have unremarkable serum biochemistry and hematology values unless urethral obstruction occurs. Urethral obstruction is associated with postrenal azotemia and electrolyte disturbances, particularly hyperkalemia, and a stress leukogram may be present. Urine should be assessed for physical appearance, routine biochemical analysis (including pH and specific gravity), microscopic examination of sediment, and bacterial culture and sensitivity. Although bacterial urinary tract infections are a rare (<1%) cause of uncomplicated FLUTD, signs of FLUTD in a diabetic cat are much more likely to be caused by bacterial cystitis. Repeated culture and sensitivity of urine may be necessary in diabetic cats suffering from lower urinary tract signs, particularly because pyuria is often not observed in these cats partly because of the dilute nature of the urine. Uroliths may be ruled out by the use of ultrasonography or contrast radiography. A diagnosis of feline idiopathic cystitis is one of exclusion; however, in the author's experience, diabetic cats are not often afflicted with idiopathic feline cystitis, perhaps because of frequent voiding caused by osmotic diuresis.

ENVIRONMENTAL AND DIETARY THERAPY

A lower-carbohydrate, higher-protein diet may ameliorate 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 58% of cats discontinue insulin injections, and those with continued insulin requirements could be regulated on a much lower dosage (1 to 2 U every 12 hours).[159] Comparison of canned high-fiber versus low-carbohydrate diets showed that cats fed low-carbohydrate diets were 3 to 4 times more likely to discontinue insulin injections.[13] The diet formulation is critical in that most dry cat food formulations contain excessive carbohydrates; therefore canned cat foods and preferably higher protein foods should be used for initial treatment of diabetic cats. Caution should be used when initially changing from dry to canned foods as insulin requirements may decrease and a reduction in insulin dosage may be required.

The aim of dietary therapy of FLUTD is to create less concentrated urine (ideally, specific gravity ≤1.035), encourage more frequent urination, and make urolith, crystal, or urethral plug formation less likely. Rather than altering the content of a dry diet, it is preferable to feed a canned diet. Diets designed with a higher protein content that promote weight loss may also be beneficial, because both diabetes mellitus and FLUTD are most often seen in obese cats. Food should be measured and fed to attain an optimal body condition score (4 to 5 on the 9-point scale or 2.5 to 3 on the 5-point scale). For cats with concurrent diabetes and lower urinary tract disease, canned food is recommended both because it contains water and because it is low in carbohydrate content.

Recent evidence suggests that signs of FIC can be reduced by the use of a multimodal environmental modification program.[33] An appropriate number and positioning of the litter boxes should allow the cats to have free access. Although covered litter boxes may be thought to provide a safe and private place to eliminate, many cats will not use them. Daily scooping of urine and feces is essential, and full cleaning of the box and replacement of the litter should take place at least once a week. This is particularly important in diabetic cats with FLUTD because of the presence of polyuria as well as possible odors. The use of Feliway (Ceva Animal Health, Buckinghamshire, England) diffusers during this process is recommended, because it has been shown to reduce signs of defensive aggression and passive withdrawal.[90]

DRUG THERAPY

Cats with diabetes mellitus should be treated with diet and insulin or possibly diet and oral hypoglycemic agents[71,190]; however, the presence of concurrent DM and FLUTD often requires intensive control of hyperglycemia. The presence of FLUTD in a diabetic cat is not necessarily an indication that the cat will not go into diabetic remission. One recent paper showed that when an appropriate ultralow carbohydrate canned diet is used in conjunction with long-acting insulin, most newly diagnosed diabetic cats have a 70% to 90% chance of remission.[156] The reader should refer to Chapters 24 and 32 for an in-depth discussion about treatment of DM and of FLUTD, respectively.

Tricyclic antidepressants have been found to be beneficial in the treatment of some humans with interstitial cystitis, and anecdotally, in a number of cats with FIC because of anticholinergic (including increasing bladder capacity), antiinflammatory (including preventing histamine release from mast cells), antiadrenergic, analgesic, and mood-altering effects.[141] Potential side effects include somnolence, urinary retention, and increased liver enzymes. Liver function should be assessed prior to starting therapy, reassessed 1 month later, and then every 6 to 12 months while the cat is on treatment. It may be difficult to determine if liver enzyme elevations are caused by the diabetes or the tricyclic antidepressant; therefore control of the DM with gradual withdrawal of the agent may be required to determine whether the liver enzyme elevation is drug induced or not.

HEART FAILURE AND CHRONIC KIDNEY DISEASE

Marie-Claude Bélanger

Myocardial disease and chronic kidney disease (CKD) are common disorders of the geriatric cat. The coexistence of heart failure (HF) and CKD is often associated with an adverse outcome, since combined cardiac and renal dysfunctions amplify progression of failure of the individual organ through a complex combination of neurohormonal feedback mechanisms.[197]

In humans, the term cardiorenal syndrome (CRS) has generally been reserved for declining renal function in the setting of advanced congestive heart failure, but recently, a more specific classification of CRS has been published.[198] In this classification, CRS is divided into five subtypes that reflect the pathophysiology, time frame, and nature of concomitant cardiac and renal dysfunction (Box 35-1). The true existence of the negative spiral of primary CKD causing cardiac dysfunction is still unknown in small animals. Except for the consequences of hypertension, CRS subtypes 3 and 4 are probably uncommon in cats. For the purpose of this chapter, CRS will refer to subtype 2, assuming that relatively normal kidneys become dysfunctional because of concomitant HF. A special focus on the therapeutic strategies of concomitant CKD and HF will be presented.

PREVALENCE

Co-morbid dysfunction of the heart and kidney has been reported to be as high as 30% to 50% in hospitalized humans.[100,161,196,209] A lower prevalence of 15% to 30% has

BOX 35-1
Classification of Cardiorenal Syndrome in Humans

Type 1: Abrupt worsening of cardiac function (e.g., acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury
Type 2: Chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive and permanent chronic kidney disease
Type 3: Abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, ischemia)
Type 4: State of chronic kidney disease (e.g., chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
Type 5: Systemic condition (e.g., diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

Adapted from Ronco F, Ronco C: Cardiorenal syndrome, current understanding, *Recent Prog Med* 100:202, 2009.

been found in dogs with mitral valve disease.[170,187] The true incidence of CRS in cats is unknown but also appears common. A study performed on 102 cats with hypertrophic cardiomyopathy reported 59% prevalence for azotemia as compared with 25% in an age-matched control population.[80]

PATHOPHYSIOLOGY

The pathophysiology of CRS is complex and not completely understood. CRS occurs when worsening renal function limits diuresis despite a clinical volume overload associated with HF. The etiology of CRS is multifactorial and involves bidirectional interactions, effects, and reactions between the heart and kidneys. It includes activation of the renin angiotensin aldosterone (RAAS) and sympathetic systems, potentiation of oxidative stress, endothelial dysfunction, and defective nitric oxide metabolism (Figure 35-2). In chronic HF, long-term reduced renal perfusion is responsible for worsening renal function. However, hypoperfusion alone cannot explain progressive renal dysfunction as the cause of

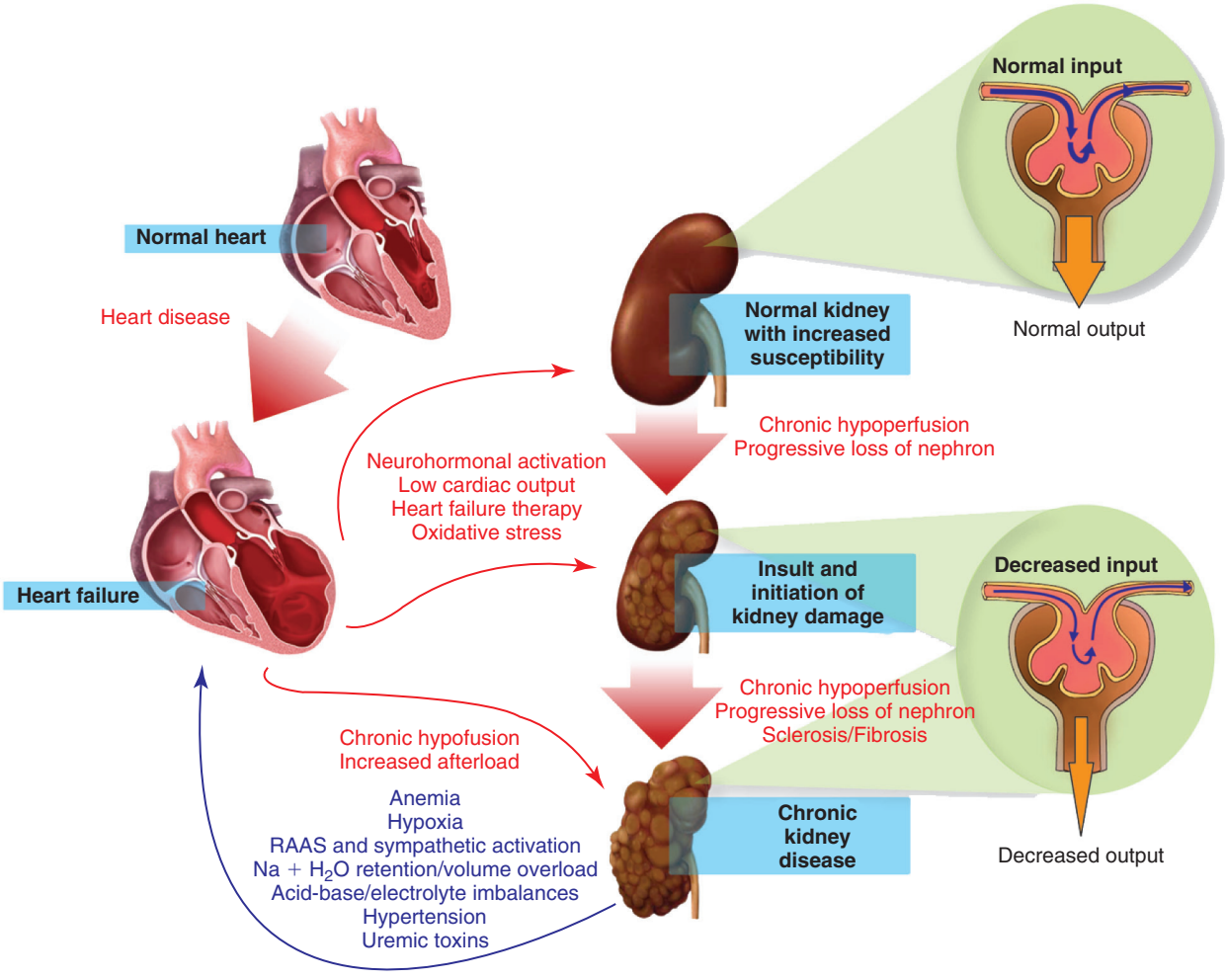

FIGURE 35-2 Pathophysiology of cardiorenal syndrome. *(Drawing by Maxim Moreau.)*

CKD. Numerous neurohormonal mechanisms are implicated and include vasoconstrictive (epinephrine, angiotensin II, endothelin), vasodilatory (BNP, nitric oxide), and inflammatory (C-reactive protein) mediators.[4] Other contributing factors include the deleterious effects of uremia and acidemia on cardiac inotropy, the hypotensive effects of diuresis-associated hypovolemia, and RAAS blockade.[164,171] Whether these mechanisms are responsible for CRS in cats remains speculative.

DIAGNOSIS

While managing a cat for chronic HF, the veterinarian should monitor for and anticipate CRS. This syndrome is suspected when worsening of renal function as determined by a decline in creatinine clearance (eventually leading to azotemia) is observed in cats treated for HF. For both medical planning and prognostic purposes, the glomerular filtration rate (GFR) should be estimated and included in the initial database. In a clinical setting, creatinine concentration can be used as an indirect, albeit insensitive, estimate of GFR. Numerous nonrenal factors affect serum creatinine levels, most notably a decline in muscle mass causes a reduction in this parameter, possibly giving a false sense of improvement in GFR.

The diagnosis of CKD is difficult in cats already being treated for HF. The diagnostic hallmark of isosthenuria in the presence of azotemia cannot be used in patients receiving diuretics, since they result in a lower USG. Also, mild or moderate prerenal blood urea nitrogen (BUN) elevation is expected in cats receiving diuretics, and a mild creatinine increase is also possible.[17,170,187] However, a progressive rise of BUN, and especially creatinine with or without a decreasing USG, in a cat treated for chronic HF should alert the practitioner to potential development of CRS. Longitudinal assessment of serum creatinine is therefore important, and a progressive rise can indicate declining renal function even when values remain in the normal range. Other indices of CKD are hyperphosphatemia, hypokalemia, nonregenerative anemia, and proteinuria. The classical clinical signs of feline CKD (e.g., increasing polyuria/polydipsia [PU/PD], inappetence/anorexia, vomiting, and weight loss; see Chapter 32) should also be considered suspicious for CRS.

To identify renal dysfunction in a cat with HF, a complete blood count (CBC), serum chemistry profile, urinalysis, and urinary protein:creatinine ratio should be determined. Abdominal ultrasonography should be performed to recognize the typical architectural changes of CKD (small kidneys with altered surface contour and poor corticomedullary distinction) and to identify underlying causes of CKD (e.g., pyelonephritis, nephrolithiasis, neoplasia, polycystic kidney disease) that may have specific treatments. Potential aortic thromboembolism resulting in renal infarction and acute decline in renal function should be considered when a cat with HF presents with acute renal failure. Urine culture should be performed to identify and treat possible urinary tract infection. Systemic blood pressure should be evaluated in cats with CRS, since the presence of hypotension will worsen renal perfusion, whereas hypertension will negatively affect cardiac output and renal function. In calm, conscious cats, a systolic blood pressure greater than 160 to 180 mm Hg should be regarded as suspect for hypertension. A complete echocardiogram is usually indicated to optimize treatment of the primary cardiomyopathy and to assess the risk for potential embolic events. Finally, thoracic radiographs should be performed to evaluate the level of control of the HF and to adjust the medical plan accordingly.

A promising tool in the diagnosis of CRS in cats is the measurement of serum amino-terminal probrain natriuretic peptide (Nt-proBNP). Indeed, this biomarker has been shown to offer powerful diagnostic and prognostic information in humans suffering from CRS.[3,235] A commercial Nt-proBNP assay is now available in cats and could eventually prove useful in the diagnosis and management of CRS in this species.

THERAPY

Treatment of CRS in cats is largely empiric, because no clinical trials have been completed. Box 35-2 summarizes the general approach to the cat presented with CRS. The goal is to recognize the syndrome, reverse it as much as possible, and deal with the renal consequences of chronic HF.

The main challenge in the treatment of co-morbid HF and CKD is trying to balance two organs with antagonistic volume needs.[47] The goal is to find a balance between the tendency to "dry-out" HF while hydrating CKD. Unfortunately, HF control is often favored to the detriment of renal support, leading to adverse long-term consequences on the kidneys. Therefore management of cats with CRS should focus on therapeutic strategies aimed at controlling signs of one organ failing while avoiding iatrogenic decompensation of the other organ. Since the degree of compromise of each organ is variable, Table 35-2 describes specific treatment plans in different CRS situations.

Optimizing Heart Failure Therapy

Angiotensin-Converting Enzyme (ACE) Inhibitors

Because of RAAS activation, angiotensin-converting enzyme (ACE) inhibitors are the mainstay of therapy for concomitant HF and CKD, especially in the presence of hypertension and/or proteinuria. Although activation of RAAS is beneficial in the early stages of renal disease,

BOX 35-2
Approach to the Cat with Cardiorenal Syndrome

1. Recognize and anticipate CRS
   - Record baseline BUN/Cr/USG/UPC ratio
   - Monitor for temporal Cr rise
2. Optimize HF therapy
   - Lowest effective dose of furosemide
     - Consider dual-diuretic therapy
     - Consider torsemide if diuretic resistance
   - ACE inhibitors
   - Other cardiac drugs
   - Thoracocentesis/abdominocentesis
3. Evaluate and monitor renal function
   - CBC/serum chemistry profile/urinalysis ± UPC ratio
     - q1-3 months or when changing treatment plan
   - Urine culture
   - Abdominal ultrasonography
4. Control hypertension
   - Assess systolic blood pressure (SBP)
   - Treat when SBP > 160 mm Hg
     - Amlodipine
5. Avoid hypotension
   - If SBP < 100 mm Hg
     - Reassess hypotensive drugs
     - Consider positive inotropes
6. Improve renal therapy
   - Omega-3 fatty acid supplementation
   - Feed renal diet if in ≥ IRIS stage 2 + sodium restriction
   - Phosphate binders
   - K^+ supplementation
   - H_2-blockers if GI signs
   - Consider long-term SC fluids
   - Consider renal replacement therapy
7. Improve cardiac output
   - Consider positive inotropes
     - Dobutamine unconvincing
     - Pimobendan promising
8. Correct anemia of CKD
   - When Hct < 18% to 20%
     - EPO administration
9. Review and modify drug dosages
   - Extend dosage interval of renally excreted drugs
   - Check for drug interactions

ACE, Angiotensin-converting enzyme; *BUN,* blood urea nitrogen; *CBC,* complete blood count; *CKD,* chronic kidney disease; *Cr,* creatinine; *CRS,* cardiorenal syndrome; *EPO,* erythropoietin; HF, heart failure; *Hct,* hematocrit; *IRIS,* International Renal Interest Society; *SBP,* systolic blood pressure; *SC,* subcutaneous fluids; *UPC,* urine protein to creatinine ratio; *USG,* urine specific gravity.

TABLE 35-2 Therapeutic Strategies in Different Cardiorenal Syndrome Situations

	Renal Dysfunction	
	Normal Cr	**Increased Cr**
HEART FAILURE		
Resolved	Find lowest effective diuretic dose Optimize follow-up	Reduce furosemide dose Reassess ACEI dosage Consider positive inotropes Stimulate water consumption Consider SC fluids
Unresolved Progressive or Severe	Increase furosemide dose Consider dual-diuretic tx Consider furosemide CRI Consider torsemide Control arrhythmias Increase ACEI dosage/frequency Consider pimobendan Consider afterload reduction: arteriodilator/amlodipine	Optimize positive inotrope Consider dual-diuretic tx Control signs of uremia Maintenance SC fluids Increase arteriodilator Control hypertension Avoid iatrogenic hypotension Consider renal replacement tx

ACEI, Angiotensin-converting enzyme inhibitors; *Cr,* creatinine; *CRI,* constant rate infusion; *CRS,* cardiorenal syndrome; *SC,* subcutaneous; *tx,* treatment.

prolonged renal ischemia exacerbates renal injury and may ultimately generate fibrosis in cats as it does in other species.[21] In CKD, ACE inhibitors limit systemic and glomerular capillary hypertension, have an antiproteinuric effect, and retard the development of glomerulosclerosis and tubulointerstitial lesions.[148] In proteinuric dogs, enalapril has been shown to counteract proteinuria and delay the onset or progression of azotemia.[82,147] ACE inhibitors have also shown to be beneficial in cats with proteinuric CKD.[26,133] Historically, some concerns have been expressed regarding the long-term effects of ACE inhibitors on renal function. However, chronic enalapril

administration does not adversely affect kidney function in dogs with mitral valve disease.[5]

Cats with CRS should be volume-repleted before being started on low-dose ACE inhibitors (benazepril or enalapril, 0.25 mg/kg, PO, every 24 hours). This dose can eventually be increased (0.5 mg/kg, PO, every 12 to 24 hours) for better control of HF. Benazepril is metabolized in the liver, whereas enalapril is metabolized by liver and kidneys. Consequently, cats with CRS might need a lower dose of enalapril than benazepril. Initiation of ACE inhibition therapy is associated with a transient decrease in GFR and increase in BUN and creatinine concentrations. Cats showing an increased creatinine or those already on an ACE inhibitor while developing renal failure, can remain on therapy. In CRS, ACE inhibitors are beneficial long-term and are generally not responsible for worsening renal function. Lowering the dosage of the ACE inhibitor is usually sufficient in this situation.

Diuretics

As a general rule, if increasing azotemia becomes a concern in cats with CRS, decreasing the furosemide dosage should be the first approach. Diuretics lower cardiac output and renal blood flow, which will tend to increase BUN and creatinine. Elevation of BUN concentration in cats treated with furosemide is mostly prerenal and generally necessary to control HF; therefore it is prudent to use the lowest effective dose of furosemide that controls the HF. The dose has to be continuously reassessed, depending on the type and progression of heart disease, dietary salt intake, and renal adaptation to the diuretic. Conversely, a very important principle when determining the ideal furosemide dosage for an individual HF patient is that the threshold rate of drug excretion must be achieved for optimal efficacy.[75] In other words, the practitioner must find the single effective dose resulting in adequate natriuresis; a cat that is nonresponsive to 5 mg of furosemide will need 10 mg (every 8, 12, or 24 hours) rather than giving 5 mg every 12 hours. Adequate natriuresis can be grossly assessed in a clinical setting by observation of increased urine volume and decreased urine specific gravity. Another important principle with regard to diuretics in CRS cats is to periodically drain pleural effusion or ascites in order to avoid excessive diuretic use.

Diuretic resistance is a phenomenon that can be seen in animals with chronic HF. It is defined as a clinical state in which diuretic response is diminished or lost before the therapeutic goal of relief from edema has been reached. Multiple factors account for diuretic resistance, including insufficient diuretic dose, excessive sodium intake, inappropriate intestinal absorption of oral drugs, increased sodium reabsorption at diuretic-insensitive sites in the nephrons, decreased renal perfusion, and urinary diuretic excretion.[199] When diuretic resistance occurs in cats with CRS, a furosemide constant rate infusion (0.3 to 0.6 mg/kg/h IV) helps to achieve effective natriuresis, since it inhibits sodium reabsorption more consistently and safely than oral or IV boluses do.[204] Once the volume-overloaded state has resolved, most cats will once again respond to oral therapy. Another strategy to consider when diuretic resistance is suspected is to switch to a different oral loop diuretic. Torsemide (Demadex) is useful in CRS patients because of its excellent bioavailability, superior diuretic action, and long half-life. A recent study on eight healthy dogs showed that diuretic resistance developed after 14 days of furosemide, but not torsemide, administration.[115] Torsemide (0.3 mg/kg, PO, every 24 hours) has been evaluated in cats with experimentally induced left ventricular hypertrophy and appears to be 10 times more potent than furosemide.[229] The diuretic effects peak at 4 hours after oral administration and persist for 12 hours. Further studies are needed to establish the dosage range in cats.

Dual-diuretic therapy can be considered when furosemide dosage needs to be decreased. Combination therapy potentiates diuretic effects by acting at multiple sites within the nephron. Spironolactone (1 to 2 mg/kg, PO, every 12 hours) should be used with caution in cats, since it may occasionally cause reversible facial dermititis.[154] Also, in the author's hands, use of aldosterone in patients with renal dysfunction sometimes causes significant hyperkalemia. Thiazide diuretics, such as hydrochlorothiazide (1 to 2 mg/kg, PO, every 12 hours), can also be used but are notably less effective than loop diuretics, especially when creatinine clearance is abnormal.

Normalizing Blood Pressure

Systemic hypertension is common in feline CKD. It complicates management of HF by increasing the afterload, consequently reducing forward cardiac output. In fact, hypertension is known to worsen both CKD and HF and should be aggressively controlled in cats with CRS. ACE inhibitors are not effective as an antihypertensive monotherapy in cats with CKD.[216] Amlodipine (0.625 mg/cat, PO, every 24 hours) should be added to the therapeutic plan as discussed elsewhere in this text. Subsequent blood pressure monitoring should be performed regularly to avoid deleterious iatrogenic hypotension, especially in a patient receiving other drugs with hypotensive effects for control of HF. Systolic blood pressure should ideally be maintained between 100 and 150 mm Hg in cats with CRS.

Improving Cardiac Output

The role of positive inotropes in feline CRS is still to be defined. Indeed, most feline HF patients are primarily

affected by hypertrophic cardiomyopathy, which is mainly a diastolic dysfunction. Nevertheless, in advanced stages of HF and CKD, use of a positive inotrope is sometimes helpful in improving renal blood flow and azotemia. Although unapproved in this species, the author has used pimobendan (Vetmedin) on several cats with end-stage CRS, resulting in improved azotemia, demeanor, and appetite. Use of pimobendan may allow a reduction in the diuretic dose. Further study is needed in this area, since a small but significant increase in BUN has been reported in dogs with HF treated with pimobendan.[78] Dobutamine (2 µg/kg/min IV) is another positive inotrope that can be used in hospitalized CRS cats, but its real benefit is still unproven.

Improving Renal Function

Management of feline CKD is discussed in detail in Chapter 32. Specific strategies to optimize renal function in CRS will be discussed in this section.

Dietary Therapy

Appropriate diet therapy is essential in the management of CRS, and nutritional needs of both cardiac and renal dysfunction should be taken into consideration. In HF, high sodium intake can prevent net fluid loss even when adequate diuresis is achieved. Therefore cats with CRS should eat a diet with a maximum sodium content of 0.25% to 0.33% (e.g., Hill's Prescription Diet k/d Feline). More stringent sodium restriction is sometimes needed in CRS cats with severe or progressive HF (e.g., Purina Veterinary Diets NF Feline Formula, Royal Canin Veterinary Diet Renal LP). Distilled or low-sodium bottled water can also be offered for drinking. Owners should be advised to avoid feeding treats with high-sodium content. Examples of low-sodium treats for cats include Purina Whisker Lickin's brands and Stewart Fiber Formula cat treats.

In CKD, dietary modification is recommended for cats in International Renal Interest Society (IRIS) stages 2 to 4. In addition to protein and phosphorus reduction, diets designed for feline CKD usually differ from maintenance diets in several ways that are also beneficial in HF: reduced sodium content, increased B-vitamin content, increased caloric density, neutral effect on acid–base balance, supplementation of omega-3 polyunsaturated fatty acids and potassium. Protein restriction should be tailored on an individual basis in cats with CRS. High-quality, biologically available proteins are important in HF to avoid loss of lean body mass. Protein should be given to the highest level tolerated by the renal dysfunction, that is, without increasing azotemia. A good option for cats with CRS is to have a homemade diet formulated to respond to individual patient needs (see Chapter 18).

Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) have many beneficial effects on both the heart and the kidney. Dietary supplementation with omega-3 PUFAs is considered renoprotective early in the course of renal insufficiency.[25] In a study of induced renal failure, dogs receiving omega-3 PUFAs supplementation had fewer structural renal lesions, less proteinuria, and preservation of GFR when compared with dogs fed a control, low-PUFA-content diet.[24] A retrospective study on the effects of several renal diets found that survival was greatest among CKD cats fed diets with the highest omega-3 fatty acids content.[184]

Omega-3 PUFAs are also beneficial in animals with cardiac disease. In one study of dogs with HF, fish oil supplementation decreased cytokine production and improved cachexia and appetite.[74] Antiarrhythmic effects of fish oil have also been reported.[130,213] Although these effects have not been studied in cats with CRS, omega-3 PUFAs can be given at the following dosages:

- Eicosapentaenoic acid (EPA): 40 mg/kg, PO, every 24 hours
- Docosahexaenoic acid (DHA): 25 mg/kg, PO, every 24 hours

Fluid Therapy

In volume-depleted CRS patients, administration of IV fluids may be essential to reduce uremia. Increasing extracellular volume with IV fluids will improve renal flow and promote fluid diuresis but may precipitate congestive heart failure. Therefore the main focus will be to determine when the euvolemic status is reached to avoid excessive fluid administration. A good strategy is to use replacement-type fluids (e.g., Plasmalyte-148, lactated Ringer solution) to slowly correct dehydration and then change to maintenance low-sodium crystalloid fluids (e.g., NaCl 0.45% with 2.5% dextrose, Plasmalyte-56 with 5% dextrose) to further improve azotemia. The rate and amount of fluids to administer must be determined on a case-by-case basis. Recording patient weight is easy and important in deciding how to adjust fluid rates. Onset of a new gallop sound, or progressive increase in the respiratory, and/or heart rate in a cat with preexisting heart disease may indicate impending congestive HF and justify fluid rate reduction. Central venous pressure monitoring and echocardiography (monitoring for left atrial dilation) are two useful diagnostic tools that can also be used to guide fluid adjustment. Although controversial, concomitant low-dose constant rate infusion (CRI) of furosemide is sometimes needed in cats with end-stage CRS.

Although there are no scientific studies to support this claim, many cardiologists consider subcutaneous fluids less likely than IV fluids to worsen signs of

congestive heart failure.[56] As discussed in Chapter 32, subcutaneous fluid administration can improve dehydration and signs of uremia in cats with CKD. This strategy is also helpful in CRS cats with worsening azotemia. Typically, a balanced electrolyte solution (e.g., lactated Ringer solution) is administered subcutaneously every 24 to 48 hours. Again, the frequency and the amount of fluids to administer should be determined on a case-by-case basis, and close monitoring for volume overload must be done. In fragile patients, it is recommended to start with a small volume, such as 30 mL every 48 hours. If the expected effect on uremia is suboptimal, the volume can cautiously be increased to 50 mL once daily. Serial assessment of hydration, uremic signs, and renal function should be done to adjust fluid therapy accordingly. Sodium-containing fluids given subcutaneously do not provide electrolyte-free water. Therefore providing water through a feeding tube is another option. This approach may be easier for the owner and can also be used to feed some anorectic CRS cats until uremia has improved.

Electrolytes should be monitored closely in CRS animals, especially potassium, because hypokalemia can trigger ventricular tachyarrhythmias and refractoriness to some antiarrhythmics. Hypokalemia can be corrected through fluid therapy (KCl 0.05 to 0.5 mEq/kg/h depending on the level of hypokalemia) or by use of oral supplementation (potassium citrate or gluconate; 1 to 4 mEq/cat, every 12 hours).

Finally, renal replacement therapy, such as hemodialysis or ultrafiltration, can improve survival and quality of life in cats with end-stage CRS. Unfortunately, availability, feasibility, and costs of renal replacement therapy are still a concern for most cat owners.

Correcting Anemia

Anemia is relatively common in cats with CKD. Several mechanisms exist: anemia of chronic disease (iron sequestration), anemia due to decreased erythropoietin (EPO) production, and anemia from inadequate protein intake for normal hemoglobin production. In humans with HF, anemia can also occur secondary to defective erythropoiesis and represents an independent risk factor for poorer outcomes.[56,116] Dogs with HF have been shown to have lower hematocrits than healthy controls.[67] Recently, in human studies, there has been a growing interest in the pathogenic link between EPO deficiency and progression of CRS. Cardiac EPO receptor activation may protect the cardiomyocytes from apoptosis, inflammation, and fibrosis.[193] Clinical studies suggest that EPO supplementation in anemic patients with CRS improves cardiac function.[175] In cats with CRS, significant anemia can be corrected with use of EPO or darbepoetin administration (see Chapter 32). Caution is advised when blood transfusions are given to normovolemic anemic cats with CRS, since it can precipitate congestive HF. Chronic gastrointestinal blood loss of CKD should also be considered and treated in anemic cats with CRS with gastrointestinal protectants such as proton pump inhibitors (e.g., omeprazole), H_2 antagonists (e.g., famotidine), or barrier protectants (e.g., sucralfate).

Reviewing and Modifying Drug Dosages

Since cats with CRS receive many drugs, it is important to review and adjust their dosage at each visit. Special care should be taken to check for drug interactions and to prolong the dosing interval of renally excreted drugs, such as atenolol, propranolol, and enalapril, since higher serum levels should be expected when renal function has decreased. However, dosage adjustments may not be appropriate for drugs that are administered to effect such as amlodipine. Hepatic biotransformation of drugs (e.g., diltiazem) can also be altered in some cats with heart failure. More information on drug dosage adjustment for certain disease states can be found in Chapter 4.

PROGNOSIS

In humans with HF, renal dysfunction is strongly linked to increased morbidity and mortality.[214] Moreover, in HF, relative to a decline in ejection fraction, a fall in GFR is a more important factor for worsening prognosis.[101] Negative predictors for development of renal failure in people with HF include old age, low cardiac output, elevated baseline creatinine concentration, progressive rise in creatinine concentration, hypertension, and diuretic and calcium channel blocker therapy.[79,138,208] In a study of cats with hypertrophic cardiomyopathy, azotemia was correlated to older age, lower body weight, and higher systolic blood pressure.[80] Although renal function may remain stable for months in cats with HF, when CRS occurs, it leads to frequent hospitalization, difficulty maintaining good quality of life, and eventually, euthanasia. The therapeutic strategies discussed above are mainly directed at improving the quality of life for cats with CRS. Whether they also contribute to prolonged survival is unknown.

MANAGEMENT OF CONCURRENT PANCREATITIS AND INFLAMMATORY BOWEL DISEASE

Debra L. Zoran

Feline inflammatory bowel disease (IBD) is a term that is applied to a number of poorly understood chronic enteropathies characterized by infiltration of the gastrointestinal (GI) mucosa with inflammatory cells.

The cellular infiltrate in the mucosa of affected cats is composed of variable populations of lymphocytes, plasma cells, eosinophils, and neutrophils that can be distributed throughout the length of the GI tract as well as all layers of the gut wall.[57,97,125,135,252] In severely affected cats, this infiltrate may be accompanied by changes in the mucosal architecture, including villus atrophy and fusion, fibrosis, and lymphangiectasia.[52,239] Although IBD is a common clinical diagnosis in cats, this is often because the term is used as a catch-all to describe all chronic GI diseases, in some cases without biopsy confirmation or an attempt to truly rule out identifiable causes of intestinal inflammation. Nevertheless, our understanding of the etiopathogenesis of feline IBD, or the local and systemic consequences of the disease, including inflammation of surrounding structures, such as the pancreas or common bile duct, is only in early stages of study.

There is increasing evidence that feline IBD is a consequence of alterations in the GI microflora and concurrent increases in proinflammatory cytokines that together result in a persistent, and ultimately aberrant, mucosal immune response.[121,123,236] To further complicate the clinical picture, an increasing number of cats with IBD are recognized (by GI function testing, ultrasound [US], and biopsy) to have concurrent inflammation (nonsuppurative or lymphoplasmacytic) extending to the pancreas, biliary tract, or both (a condition termed triaditis).[55,228,241,242] Thus although IBD is beginning to be characterized beyond the visible changes in gross histopathology, it is also clear that the idea that IBD is a chronic enteropathy with no relationship to the other two common inflammatory diseases of the feline abdomen (cholangitis and pancreatitis) is not consistent with current evidence. This paper will briefly review the key studies that have furthered our understanding of these diseases, and then focus on the current best recommendations for therapy of cats with concurrent IBD and pancreatitis.

UNDERSTANDING WHY INFLAMMATORY BOWEL DISEASE AND PANCREATITIS OCCUR TOGETHER

One of the most important areas of investigation in current IBD research is seeking to understand the role of enteric microflora in the pathogenesis and immune dysfunction of the disease. In recent work by Janeczko and coworkers, intestinal biopsies were collected from 17 cats undergoing diagnostic investigation of signs of GI disease and from 10 healthy controls.[123] Subjective duodenal histopathology ranged from normal (n = 10) to mild (n = 6), moderate (n = 8), or severe (n = 3) IBD. The number and spatial distribution of mucosal bacteria were determined by fluorescent in situ hybridization (FISH) with probes to 16S rDNA. The mucosal response was evaluated by objective histopathology and cytokine mRNA levels in duodenal biopsies. The number of mucosa-associated Enterobacteriaceae was higher in cats with signs of GI disease than in healthy cats.[123] These pathogens, including *Escherichia coli* and *Clostridium* species, were associated with significant changes in mucosal architecture, principally atrophy and fusion; upregulation of cytokines, particularly interleukin-8 (IL-8); and the number of clinical signs exhibited by affected cats.[123] The study findings indicated that an abnormal mucosa-associated flora is associated with the presence and severity of duodenal inflammation and clinical disease activity in cats.[123]

Additional evidence that bacteria are a key component of IBD in cats is shown in an earlier study by Inness and coworkers, who characterized the gut microflora of both healthy cats and cats with colonic IBD using FISH techniques.[121] In this study, cats with colonic IBD were found to have significantly higher populations of *Desulfovibrio* (a genus of bacteria that produce toxic sulfides) compared with normal cats, which had higher populations of bifidobacteria and bacteroides (normal flora).[121] These authors proposed that modulation of intestinal flora with probiotics and dietary intervention to decrease the production of pathogenic bacteria were likely important in treating cats with IBD. These early studies corroborate the findings in numerous human and rodent studies on IBD that the intestinal microbiome is a key factor in maintenance of the health of the GI tract and can be the focal point of inducing an inflammatory response that results in development of IBD and gut dysfunction.[1,63,73] The importance of these findings for clinical management of cats with IBD is to develop a better understanding of intestinal dysbiosis (imbalance of the intestinal microflora) and its potential role in IBD.

One of the major risk factors for development of any form of pancreatitis in cats is concurrent GI disease and particularly IBD.[240-242] In a recent study, approximately 20% of cats with biopsy confirmed pancreatitis had concurrent IBD.[241] In addition, a recent retrospective of feline necropsies revealed evidence of chronic lymphocytic plasmacytic (LP) pancreatitis in 60% to 65% of the specimens—whether or not they had been previously diagnosed with pancreatic disease.[55] This study revealed that many cats have histopathologic evidence of pancreatitis even in the absence of a clinical diagnosis, thus pointing out that an awareness of this often subclinical problem is paramount to looking for it in cats with IBD.

There are certain factors that may contribute to the increased risk of concurrent pancreatitis in cats with IBD: (1) IBD is a common cause of GI disease in cats and the signs of GI disease and pancreatic disease can overlap, so, differentiation of the two can be difficult and (2) the pancreatic and biliary duct anatomy of the cat allows ready access of duodenal fluid that may be

refluxed during vomiting or abnormal duodenal motility. Unlike the dog, the feline pancreaticobiliary sphincter is a common anatomic channel at the duodenal papilla. As a result, reflux either from the biliary tree or the duodenum will affect the pancreatic ductal system.[240] In the case of concurrent IBD, the fluid entering the ductal system likely contains a higher number of pathogenic bacteria (or at least an imbalance), bile salts, and activated pancreatic enzymes that when allowed to perfuse the pancreas and biliary tree results in varying degrees of tissue damage, infection, and inflammation.[240,250] In addition to reflux from vomiting, abnormal GI motility and immune dysregulation are likely important in both the reflux of intestinal contents into the pancreatic ducts and development of the inflammation.[240] In summary, although more studies are required to better understand the pathogenesis of concurrent IBD and LP pancreatitis, it is clear that this phenomenon presents an important clinical problem that feline practitioners must try to identify and manage.

MANAGEMENT OF CONCURRENT INFLAMMATORY BOWEL DISEASE AND PANCREATITIS IN CATS: START WITH INFLAMMATORY BOWEL DISEASE THERAPY

Treatment of cats with IBD has not changed significantly for years: antiinflammatory or immune-suppressive therapy with corticosteroids or drugs such as chlorambucil or cyclosporine (if the cat is corticosteroid intolerant or has severe disease not controlled by the corticosteroids), use of antimicrobials with immune-modulating characteristics (e.g., metronidazole or tylosin), and dietary modification aimed at improving the digestibility and reducing the food-related antigens or factors that may induce intolerance.[227] In humans, IBD therapy has also included the use of antibiotics with immune-modulating capacity, prebiotics, probiotics, and immunosuppression, as well as other drugs that modify cytokine release.[1] Unfortunately, studies assessing therapeutic modulation of enteric flora (using probiotics, prebiotics, or other specific therapy for cytokines) in cats with IBD have not yet been reported. Nevertheless, management of IBD in cats will continue to evolve as more studies reveal the importance of therapy that is focused on the normalization of the intestinal microbiome and more specific suppression of cytokines (e.g., dietary therapy, prebiotics, probiotics, and antiinflammatory drugs that are targeted to the GI tract). For detailed, specific information on the management of IBD in cats, please see Chapter 23. Finally, no matter what approach is used, because the disease is so variable and many causative factors are involved, a staged approach to therapy (when possible) is suggested. Sequential clinical treatment trials with antiparasiticides, dietary therapy, and antibacterials (including prebiotics and probiotics) should be tried before initiating immunosuppressive therapy if possible.

GASTROINTESTINAL FUNCTION TESTING IN PLANNING THERAPY

The important role of cobalamin in normal function of the GI tract and in many other aspects of metabolism is well documented.[201,202] In addition, the diagnostic and therapeutic utility of measuring serum concentrations of cobalamin and folate in cats with suspected intestinal disease is also well established.[201,211] However, in cats with IBD that may also have pancreatitis, specific testing for pancreatic leakage and function should be included in the evaluation: feline pancreatic lipase immunoreactivity (fPLI) and feline trypsin-like immunoreactivity (fTLI) are two important tests to perform. Although there are a number of issues associated with the diagnosis of feline pancreatitis and many limitations of fPLI (see Chapter 23), it remains the test of choice for documenting the presence of enzyme leakage from the pancreas and should be measured in all cats with IBD.[72,250,257]

The fTLI test is the diagnostic test of choice for exocrine pancreatic insufficiency (EPI), and although EPI is currently not commonly recognized in cats, it does occur secondary to chronic pancreatitis and results in weight loss (the most common sign), diarrhea, and poor thrift in affected cats.[217,225] This is a relevant problem, because each of those clinical signs can be confused with uncontrolled or recurrent IBD. The repeated monitoring of fTLI, in addition to cobalamin and folate, are important in the management of cats with concurrent IBD and pancreatitis, because cats without deficiencies at the time of diagnosis may develop them later. Comprehensive therapy of concurrent IBD and pancreatitis requires both recognition and correction of these potential enzyme and vitamin deficiencies.

THE ROLE OF DIETARY MANAGEMENT: FOCUS ON THE GASTROINTESTINAL TRACT

The use of diet in the management of GI or pancreatic disease is not a new concept, but the question of which type of diet to use has become an increasingly complex issue. Additionally, there is no evidence in cats with pancreatitis (as there is in dogs) to suggest that dietary fat levels (or any other dietary component) are involved in the pathogenesis of the disease. Thus two key points must be made at the outset: (1) Cats with pancreatitis should not be held NPO, because this increases the risk of development of hepatic lipidosis and is detrimental

to GI health and function, and (2) current recommendations for cats with pancreatitis are to focus on finding an appropriate diet for management of the IBD, because control of this disease may result in an improvement in the pancreas as well.[240,250,257]

Although there are few dietary recommendations for cats with pancreatitis, there have been a number of studies and reviews discussing the role of diet in the development and management of IBD.[89,143,227,254] However, the influence of diet type and composition occurs first in healthy, normal cats, because the diet fed is a major determinant of the intestinal microbiome and specifically determines both the numbers and species of bacteria that populate the intestinal tract.[7,66,194,230] Further, the influence on the microflora that occurs because of diet changes can be profound when a major change occurs (e.g., high carbohydrate to high protein, dry to canned food). Thus changes in diet should be done slowly (over days or longer), with careful assessment of progress (especially monitoring for clinical deterioration). Ideally, probiotic therapy should be added to reduce the probability that major shifts in the microbiome will occur as a result of overgrowth of pathogens.[155] Finally, although diet changes have a significant influence on the microflora of healthy cats, this effect can be even more profound in cats with an abnormal flora (such as occurs in cats with IBD). Thus when planning dietary therapy in cats with IBD, there are three critical areas where, because diet may be the inciting cause of the inflammation, correction can influence therapy: (1) diet effects on microbiome (e.g., dysbiosis, or disruption of the microflora), (2) dietary intolerance (nonimmunologic effects on gut function and microbiome), and (3) true dietary allergy. To address these possible causes of diet-induced GI inflammation requires food trials (of varying lengths) using diets aimed at correcting the possible problem. Unfortunately, there is no single diet, or series of diets, or even family of diets that can address each of these potential problems across all cats; it is a process of elimination for the individual patient. The interested reader is referred to Chapter 17 for a review of the approaches that can be used to make a diagnosis of food allergy.

The remainder of this section will focus on the issues of diet intolerance and dysbiosis—difficult to identify but believed to be the most common reasons for diet-induced inflammation in cats.[89,123,143] In many, if not most, cats with mild IBD, especially those with a mild to moderate infiltrate of inflammatory cells and without significant weight loss, the initial approach should be to feed a highly digestible diet (this could include novel or hydrolyzed diets) with single-source meat protein, low amounts of highly digestible carbohydrates, and fewer additives, flavorings, or other substances that may be associated with poor digestibility or food intolerance.[256] Although diets with a high digestibility are not defined in a regulatory sense, this is generally a product with protein digestibility of greater than 87% (typical diets are 78% to 81%) and fat digestibility of greater than 90% (typical diets are 77% to 85%).[256]

The protein digestibility of a diet is one of the key factors that can determine its success in cats with IBD, primarily because undigested protein is a recognized food source for pathogenic bacteria, and can be associated with toxic products in the GI tract that can increase disruption of the microbiome. As a general rule, meat-source proteins (including meat meals) are more digestible than plant-source proteins (there are some exceptions, such as soy), and animal proteins are more digestible than meat byproducts. Further, in cats with IBD, the type and amount of carbohydrates added to the diet must also be considered, since malabsorption of carbohydrates can occur without causing clinical signs.[54,230] To address this, diets with a single carbohydrate source are preferable to foods with many different sources, and highly digestible carbohydrate sources are better than complex grain source carbohydrates (e.g., wheat or corn).[256]

It is important to recognize that when one diet from this category is not accepted by the cat or does not improve the clinical signs, it cannot be assumed that all diets in this category will not be accepted by the patient or will be ineffective. Many different brands fall under the category of "highly digestible," but they are not all alike and will not necessarily have the same effect in all cats. The formulation of highly digestible diets from different pet food manufacturers is quite variable, with different protein and carbohydrate sources and amounts and different amounts of fat; also some of the diets may contain various additives designed to promote intestinal health (e.g., fructo-oligosaccharides [FOS], mannosoligosaccharides [MOS], omega-3 fatty acids, antioxidant vitamins, and soluble fiber). If one type of highly digestible diet has been fed for at least 2 weeks with minimal response, then it is entirely reasonable to try another diet from the same category, but from a different manufacturer or try an entirely different dietary strategy (e.g., high-protein/low-carbohydrate novel antigen, hydrolyzed diet). As previously mentioned, because changes in diet type and source can result in significant changes in the intestinal microbiota, the addition of probiotics or prebiotics as part of the therapy is reasonable to help prevent further disruption of the microflora.[155]

NORMALIZING THE MICROBIOME: ANTIBIOTICS AND PROBIOTICS

Although correction of the diet is a key step in normalizing the intestinal microbiome, it may not be sufficient to suppress the pathogenic species that have overpopulated the intestinal lumen. As a result, antibiotic therapy with metronidazole has been effectively used for a

TABLE 35-3 Table of Dosages for Drugs Commonly Used in Feline Pancreatitis and Inflammatory Bowel Disease*

Drug Name	Role	Dosage
Prednisolone/Methylprednisolone 5- or 20-mg tabs/2- or 4-mg tabs	Antiinflammatory and immunosuppressive	1-2 mg/kg, PO, q12-24h
Budesonide (3-mg capsules)	Antiinflammatory: high first-pass metabolism	0.125 mg/kg, PO, q8-12h
Buprenorphine (0.3 mg/mL injectable)	Opioid pain reliever	0.005-0.01 mg/kg, SC, q8h 0.01-0.02 mg/kg, PO, q12h (buccal)
Metronidazole (250-mg tabs, 50 mg/mL suspension)	Antibiotic Immunomodulator	5-15 mg/kg, PO, q12h
Tylosin (2.5-2.7 g/tsp)	Antibiotic	7-15 mg/kg, PO, q12-24h
Chlorambucil (2-mg tabs)	Immunosuppressive	0.1-0.2 mg/kg, PO, q24h once then q48h (monitor CBC)
Cyclosporine (10-, 25-, 50-mg capsules, 100 mg/mL solution)	Immunosuppressive	5 mg/kg, PO, q12h, can reduce to q24h or q48h as clinically indicated
Cyproheptadine (4-mg tabs)	Appetite stimulant	2-4 mg/cat (½ or 1 tablet), PO, q12h
Mirtazapine (15-mg tabs)	Appetite stimulant	⅛ tablet, PO, q3d
Ursodiol (250-mg tabs)	Tertiary bile acid Antiinflammatory	5-15 mg/kg, PO, q24h
S-Adenosylmethionine (SAMe) alone or with Marin (milk thistle) (90-mg tabs)	Antioxidant Antiinflammatory nutraceutical	90 mg/cat, PO, q24h

*Doses from: Papich MG: *Saunders handbook of veterinary drugs*, ed 2, St Louis, 2007, Elsevier.
CBC, Complete blood count.

number of years and continues to be recommended in the therapy of IBD (Table 35-3).[227] A number of other antibiotics have been used empirically in management of feline intestinal disease, but there is no current evidence to indicate the use of other antibiotics that are directed at gram-negative or other bacteria. In fact, frequent use of broad-spectrum antibiotics will result in a further disruption of the microbiome that may contribute to worsening of the inflammation and dysbiosis, rather than improving the situation.

In cats with LP pancreatitis concurrent with IBD, any infection that occurs in the pancreas will be an extension of the flora in the small intestine and thus should be treated with antibiotics appropriate for IBD. At this time, the only form of IBD that is known to be caused by a specific bacterial species is Boxer colitis, which is caused by an enterotoxigenic form of *E. coli*.[210] In that disease, specific antibiotic regimens are suggested based on targeting therapy toward controlling that specific bacterial infection, and in Boxer dogs, complete resolution of the disease is expected by appropriate antibiotic therapy. In feline IBD, however, multiple and different bacterial pathogens have been identified in affected cats[121,194]; so, although bacterial disruption is still believed to be the trigger for the inflammatory disease process, specific antibiotic therapy is currently not recommended, and the therapeutic approach must be aimed at normalizing the intestinal microbiome by other means.

One of the reasons that metronidazole is effective in cats with IBD is likely not only because of its antibacterial properties but also because of its immune-modulating properties.[231] However, because metronidazole may be poorly tolerated and has significant potential for serious adverse effects, including neurotoxicity and reversible DNA damage in intestinal cells, it should not be given indefinitely.[206] The current recommendation is to use metronidazole for no longer than 2 to 3 weeks at a time, then stop therapy for at least several weeks to prevent accumulated DNA damage.[206] An alternative to metronidazole therapy in cats with IBD is tylosin; however, less is known about the effects of tylosin in cats with IBD or if it also has immune-modulating effects in cats, as it appears to have in dogs.[219]

Interest in the role of probiotics in prevention or treatment of gastrointestinal disease in humans and animals has been the most widely known aspect of their long history. Human and experimental studies with probiotics have targeted specific health benefits associated with three functional areas of the gut microbiota: metabolic effects, protective effects, and trophic effects.[155] The *metabolic* effects of probiotics refer to their effects on digestion, particularly in digestion of lactose and other disaccharides, and in the production of intestinal gas, a significant problem in patients with irritable bowel syndrome (IBS). Some microbial species produce large amounts of gas, and other species consume gas

particularly hydrogen; however, it is this balance that reflects the amount, frequency, and odor of intestinal gas production. To date, it appears that bifidobacterial species have the highest rates of therapeutic benefit in adult humans with IBS.[73] However, in a study in colicky infants, a *Lactobacillus* strain resulted in the greatest reduction in intestinal bloating and gas.[73] These different responses highlight the complexity of interactions among the microflora in each unique ecological habitat and emphasize the need to be cautious in predicting specific responses in individual subjects.

The *protective* effects of probiotics on the gastrointestinal tract include the prevention and treatment of acute diarrhea due to antibiotics or infectious enteritis and prevention of systemic infections (septicemia) from bacterial translocation.[73,88] There have been a plethora of clinical trials studying the efficacy of probiotics in the treatment of acute diarrhea in adults (e.g., infectious diarrhea, traveler's diarrhea); however, the evidence is most compelling for the administration of probiotics to decrease morbidity in people with antibiotic-associated diarrhea.

The third important area of probiotic influence in the gastrointestinal tract is their *trophic* effects on mucosal immunity and epithelial cell growth. Three specific conditions fall under this umbrella: inflammatory bowel disease (IBD), food allergy, and colon cancer. It is well known that certain bacteria activate proinflammatory mucosal responses, while others downregulate intestinal inflammation. Thus creating a favorable local microecology has been hypothesized to restore homeostasis of the local immune response and would lead to resolution of the intestinal inflammation.[73,88] Although evidence in humans with IBD supports the use of probiotics, there are no similar studies in cats with IBD or other chronic enteropathies.[155] Thus, although probiotic therapy in cats with IBD would be a reasonable therapeutic option, there have been no studies reported to date that identify the best probiotic species or combination of species to use or that show benefit from adding probiotics to the therapeutic plan.

CONTROL OF INFLAMMATION IN PANCREATITIS AND INFLAMMATORY BOWEL DISEASE

Both IBD and pancreatitis are inflammatory diseases for which interruption of the inflammatory process is an important part of the clinical management.[227] However, that being said, there are no studies that have carefully assessed the effectiveness of corticosteroid therapy in treatment of LP pancreatitis in cats. Thus recommendations to use corticosteroid therapy in the treatment of chronic pancreatitis in cats are anecdotal. The most effective antiinflammatory or immunosuppressive drugs for IBD (and presumably pancreatitis) are corticosteroids (i.e., prednisolone or methylprednisolone) or other drugs that interrupt the proinflammatory pathways that are active in the gut (e.g., cytotoxic drugs, such as chlorambucil or cyclosporine).[81,227] Prednisolone is more reliably metabolized than prednisone in cats; therefore the former should be chosen for therapy.[81] Dexamethasone is also effective, but is associated with a much higher incidence of severe adverse events, including intestinal ulceration; so, routine use is not recommended.

However, as is well known, chronic therapy with corticosteroids can result in development of significant insulin resistance, the major precursor to diabetes in obese cats or cats with pancreatitis. Thus alternatives to prednisolone, such as budesonide may also be a reasonable choice. There are no studies showing efficacy of this agent in cats; anecdotal reports suggest variability in clinical response. Alternatively, in cats in which corticosteroids are not effective or are causing additional morbidity, other immunosuppressive drugs may be necessary. The two drugs most commonly recommended and effective for cats in this setting are chlorambucil and cyclosporine. Chlorambucil is the best first choice based on its long record of use in IBD, and although adverse effects such as bone marrow suppression are possible, they are unlikely due to the low frequency of administration (once every 2 to 3 days, PO), also making it attractive for patient management and client compliance.[227] Cyclosporine therapy for cats with IBD has not been studied extensively, but it must be given every 12 hours, is much more expensive, and drug levels must be measured to prevent toxicity and ensure therapeutic dosing levels. Thus cyclosporine is not recommended unless the IBD is severe and unresponsive to other therapy. Whatever therapeutic options are chosen, it is important to use antiinflammatory or immune suppressive therapy judiciously (but long enough) and at the lowest doses necessary to achieve clinical control.

OTHER CONSIDERATIONS IN THERAPY OF PANCREATITIS AND INFLAMMATORY BOWEL DISEASE

In addition to antiinflammatory therapy, modulation of bacteria and dietary therapy for management of cats with concurrent IBD and pancreatitis, there are several other adjunctive therapeutic options that may be important and/or even essential. The first is careful consideration of adding pain therapy into the treatment regimen. It is well known that acute pancreatitis is a painful disease[218]; opioid analgesics are the most appropriate drugs used to control this pain.[240,250] However, because LP pancreatitis is a chronic disease, and may have only focal or low-grade inflammation, this low-grade pain may be difficult to detect.[240,250] In humans with chronic

pancreatitis, a disease with a similar presentation and clinical course, low-grade upper quadrant pain is common, and results in lack of appetite and general malaise.[218] Pain in people with pancreatitis that does not resolve with antiinflammatory therapy is frequently managed with either opioid medications or biliary stenting.[218] The key point is that cats may have low-grade pain that is manifested by hiding, decreased appetite, or even occasional vomiting, and thus use of opioid pain medications is indicated (see Table 35-2).

In addition to symptomatic therapy for pain in cats with pancreatitis, use of ursodeoxycholic acid (ursodiol) therapy can be beneficial by improving bile flow, preventing sludging, and reducing inflammation of the biliary tree and pancreas.[183,250] Further, in cats that are intolerant of steroid therapy for control of inflammation, addition of antioxidant and antiinflammatory nutraceuticals into the therapeutic plan can be potentially beneficial. Although no controlled studies evaluating the effectiveness of S-adenosylmethionine (SAMe) therapy in feline pancreatitis or IBD have been performed, studies in cats with liver disease reveal significant increases in liver glutathione concentrations and improvement in liver enzyme levels.[41] This antioxidant nutraceutical is commonly used in humans with chronic pancreatitis and IBD, and thus may also be a reasonable adjunctive therapy in cats.

Finally, because many cats with chronic pancreatitis have bouts of inappetence or decreased appetite, appetite stimulants may be indicated to encourage eating and prevent the need for placement of a feeding tube (see Table 35-2). Mirtazapine therapy in cats is very convenient, because dosing is only needed every 3 to 4 days because of its long half-life. One note of caution about use of mirtazapine in cats is advised, because some cats display significant mood changes or even hyperactivity; so, starting with the lowest possible dose is strongly suggested. Regardless of the appetite stimulant used, calculation of the daily nutritional requirements should be undertaken as well as monitoring the actual amount of food eaten.

CONCLUSION

Management of concurrent IBD and pancreatitis in cats can be a challenge, especially in cats that become diabetic or intolerant of steroid therapy. As in all chronic disease management, the goal of therapy is improving the cat's quality of life by controlling the severity of the disease while aiming for clinical remission. Control of both of these conditions is best achieved by using a combination of dietary therapy, drug therapy as needed, and frequent monitoring of progress. However, each cat will present individual challenges that require the clinician to make adjustments in the therapeutic approach. Also, because cats with chronic pancreatitis can develop diabetes or EPI as a result of progressive loss of functional pancreatic tissue, frequent re-evaluation of GI function testing and clinical response is essential to long-term success.

CHRONIC KIDNEY DISEASE AND HYPERTENSION

Scott A. Brown

PREVALENCE

Chronic kidney disease (CKD) is common in cats, particularly those greater than 10 years of age.[140] Approximately 20% of cats with CKD exhibit elevations of systemic arterial blood pressure (AP),[221] which may contribute to clinical signs, damage tissues and organs, and enhance the rate of progression of CKD.

THE KIDNEY: CAUSE OF HYPERTENSION OR A TARGET ORGAN?

The cause of systemic hypertension in a cat with CKD is usually unknown, although altered handling of fluids and electrolytes by the kidney, as well as alteration in the renin-angiotensin-aldosterone axis (RAAA) and sympathetic nervous system overactivity are potential contributory factors.

Chronically sustained elevations of AP produce injury to tissues; the rationale for treatment of hypertension is to minimize or prevent this injury, which occurs in the kidney, eyes, brain, and/or cardiovascular system.[22] Damage that results from the presence of sustained high AP is commonly referred to as end-organ or target-organ damage (TOD), and the presence of TOD is generally a strong indication favoring antihypertensive therapy. In CKD, the renal microcirculation is more susceptible to barotrauma from elevated AP because of the afferent arteriolar vasodilation that occurs in cats with renal azotemia.[23] In the kidney, TOD is generally manifest as an enhanced rate of decline of renal function, proteinuria, and/or increased mortality rate.[18,27,65,186] Proteinuria is directly related to degree of elevation of AP and rate of decline of kidney function, while inversely related to efficacy and benefit of antihypertensive therapy.[70,186]

RELATIONSHIP OF SYSTEMIC ARTERIAL PRESSURE TO RISK AND INTERNATIONAL RENAL INTEREST SOCIETY CLASSIFICATION

The International Renal Interest Society (IRIS) has proposed that a staging system be used to facilitate the management of feline patients with CKD (see Chapter

32).[65] This classification scheme is based on a three-step process:

- Establish a diagnosis of CKD
- Establish the stage of the disease[168]
- Establish the substages of the disease based on assessment of AP and proteinuria as systemic hypertension and proteinuria may be observed in any stage of CKD

Thus for all cats with CKD, AP measurement and quantification of urinary protein excretion should be performed. This allows the veterinarian to stage the disease properly, linking to prognosis[18] and diagnostic as well as treatment recommendations.[65]

SUBSTAGING CHRONIC KIDNEY DISEASE ON BASIS OF SYSTEMIC ARTERIAL BLOOD PRESSURE

Cats with CKD frequently exhibit elevations of AP.[221] The American College of Veterinary Internal Medicine (ACVIM) Consensus Statement[22] and IRIS[65] have proposed that the risk of TOD is directly related to the degree of AP elevation and have defined systemic hypertension as any elevation of AP that leads to TOD and proposed blood pressure ranges associated with minimal (AP0), low (AP1), moderate (AP2), and severe (AP3) risk of TOD (Table 35-4). A "c" is added to the AP stage if complications (TOD) are present. A notation of "nc" would indicate no complications (TOD) are present. However, kidney disease is generally presumed to be evidence of TOD in cats so that all hypertensive cats with CKD should be denoted as "c". A (T) is added to the substage if the AP measurement was obtained while the cat was receiving antihypertensive therapy.

The IRIS recommends that AP be measured using a device and method individualized for each clinical practice in every cat with CKD and that all target organs be carefully evaluated for the presence of TOD complications.[65] Although some devices provide both systolic and diastolic AP, staging is most often done on the basis of systolic AP measurements, because recent evidence suggests that systolic hypertension is the most important determinant of TOD in other species.[22] Although it is critical for the veterinarian to fully appreciate the subtleties of AP measurement, it is generally preferred to have these measurements obtained by a skilled animal health technician who has been suitably trained. The AP may be affected by stress or anxiety associated with the measurement process, the so-called white-coat effect.[12] It is important for the room in which the measurement is performed to be quiet and for the patient to have 5 to 10 minutes to acclimate to the room prior to evaluation to reduce the likelihood of this anxiety-induced hypertension.

TABLE 35-4 Arterial Blood Pressure (AP) Substaging of Feline Chronic Kidney Disease

	Substage			
	AP0 (Minimal or no risk)	**AP1 (Low risk)**	**AP2 (Moderate risk)**	**AP3 (High risk)**
BLOOD PRESSURE (MM HG)				
Systolic	<150	150-159	160-179	≥180
Diastolic	<95	95-99	100-119	≥120

If blood pressure is not measured, the patient is classified as risk not determined (RND).
If complications of high AP are present, a "c" is appended to the substage. If absent then "nc" indicates no complications have been observed. Complications include any evidence of target organ damage in eyes (e.g., intraocular hemorrhage or retinal detachment), central nervous system (e.g., seizures or profound otherwise unexplained depression), cardiovascular system (e.g., congestive heart failure), or kidneys (e.g., azotemia or proteinuria).
If antihypertensive therapy is instituted, subsequent staging of hypertension should be based on the current actual blood pressure, with (T) appended to indicate that this level reflects the effects of therapy.
For example, if a cat with chronic kidney disease (CKD) that presented with a systolic AP of 185 mm Hg (AP substage of AP3c) was treated with the calcium channel blocker amlodipine, and is now being re-evaluated and the systolic AP is 145 mm Hg, the cat's new AP substage is AP0c (T). Here the "c" reflects the presence of complications (i.e., chronic kidney disease, which is always presumed to represent a complication of hypertension), and the (T) indicates that the second set of AP measurements was taken while the cat was on antihypertensive therapy.

The choice of device depends upon operator experience and preference. For indirect devices, the cuff width should be 30% to 40% of the circumference at the chosen measurement site.[22] Measurements may be taken on the antebrachium, brachium, tarsus, or tail. The position of the patient and cuff should be one that is well tolerated with the cuff at, or close to, the level of the right atrium. At least five consecutive, consistent indirect values should be obtained with adequate time between each arterial occlusion. The highest and lowest values are then discarded and the remaining values averaged to produce the actual measurement. Because hypertension in cats with CKD is often a silent condition requiring vigilance and lifelong therapy, it is important to be absolutely certain about the diagnosis: a single high AP measurement may represent true hypertension or white-coat (anxiety-induced) hypertension. Except in the case of rapidly progressive hypertensive crises, multiple measurements should be obtained, preferably separated by at least 24 hours, and always accompanied by a thorough search for TOD before a diagnosis of systemic hypertension is established.

SUBSTAGING CHRONIC KIDNEY DISEASE ON BASIS OF PROTEINURIA

Recent findings have suggested that renal protein leak is not only a marker of severity of renal disease but also of prognostic value in animals treated with

TABLE 35-5 Proteinuria Substaging of Feline Chronic Kidney Disease

	Substage		
	Nonproteinuric (NP)	**Borderline Proteinuric (BP)**	**Proteinuric (P)**
Urine protein-to-creatinine ratio (UP/C)	<0.2	0.2-0.4	>0.4

If antihypertensive or antiproteinuric (e.g., restricted protein diet) therapy is instituted, subsequent staging of proteinuria should be based on the current actual UP/C, with (T) appended to indicate that this level reflects the effects of therapy.
For example, suppose a cat with chronic kidney disease (CKD) has a systolic AP of 140 mm Hg (AP0, no antihypertensive therapy indicated). However, the UP/C was 0.8, and thus the proteinuria substage was P. You decided to try to reduce the magnitude of the proteinuria by feeding the cat a protein-restricted diet that is supplemented with fish oil and to administer the angiotensin-converting enzyme inhibitor, benazepril. It is now being re-evaluated and UP/C is 0.3. The proteinuria substage is now BP (T) for borderline proteinuric while on therapy.

TABLE 35-6 Oral Agents for Chronic Antihypertensive Therapy in Cats with Chronic Kidney Disease

Class	Drug (Examples of Trade Name)	Usual Oral Dosage
Angiotensin-converting enzyme inhibitor	Benazepril (Lotensin, Fortekor)	0.5-1.0 mg/kg q24h
	Enalapril (Vasotec, Enacard)	0.5-1.0 mg/kg q24h
Calcium channel blocker	Amlodipine (Norvasc)	0.1-0.5 mg/kg q24h
Aldosterone antagonist	Spironolactone (Aldactone)	1.0-2.0 mg/kg q12h
Direct vasodilator	Hydralazine (Apresoline)	2.5 mg/cat q12-24h
Alpha$_1$ blocker	Prazosin (Minipress)	0.25-0.5 mg/cat q24h
	Phenoxybenazime (Dibenzyline)	2.5 mg per cat q8-12h or 0.5 mg/cat q24h
	Acepromazine (PromAce)	0.5-2 mg/kg q8h
Beta blocker	Propranolol (Inderal)	2.5-5 mg/cat q8h
	Atenolol (Tenormin)	6.25-12.5 mg/cat q12h

antihypertensives.[27,124,223] Proteinuria is associated with increased risk of developing end-stage CKD in cats,[223] and there is an increased risk of mortality in aged cats when proteinuria is present. Further, studies have shown that therapies that reduce the magnitude of proteinuria are often beneficial to the patient and may slow progression of CKD.

According to IRIS recommendations, proteinuria should be assessed in all cats with CKD (or systemic hypertension). A positive finding of proteinuria in a urinalysis with routine dipstick evaluation is the first step, which should lead the veterinarian to carefully evaluate the urine sediment findings to determine if inflammation or infection may be the cause. Because of frequent false positives with routine urine dipsticks in cats, a positive result should be confirmed by a more specific test for proteinuria that provides information on the magnitude of proteinuria, such as measurement of the urine protein/creatinine ratio (UP/C) or quantitative assessment of albuminuria. When monitoring a feline patient with renal proteinuria, it is important to determine if the proteinuria is transient or persistent (at least two tests at 2-week intervals) because only the latter justifies the institution of therapy.

Substaging of renal proteinuria should be performed in all cats with CKD (Table 35-5).[65,147] A (T) is added to the substage if the measurement was obtained when the cat was receiving antihypertensive or antiproteinuric (e.g., restricted protein diet) therapy. If persistent renal proteinuria is present in a patient with CKD and hypertension, further management is generally based on the UP/C and AP measurements.

Complete IRIS staging of a cat with CKD should reflect the IRIS stage and as well as substage for both AP and proteinuria. For example, if a cat with IRIS stage III CKD that is being treated with antihypertensive agents is re-evaluated and retinal hemorrhages are observed, the systolic AP is 165 mm Hg and the UP/C is 0.5, then the cat is IRIS stage III AP2c P (T). Here the "c" reflects the presence of complications of hypertension (i.e., proteinuria, azotemia, and retinopathy), and the (T) indicates that the measurements have been taken while the cat is on antihypertensive therapy.

EMERGENCY THERAPY: HYPERTENSIVE CRISES

Hypertension generally damages tissues by a slow, insidious process and is rarely an urgent situation. This is always the case for renal injury in cats with CKD. However, emergency antihypertensive therapy may be indicated when a cat is AP2c or AP3c and there is ocular or neurologic TOD that is likely to produce significant permanent abnormalities without rapid lowering of AP (e.g., seizures or retinal detachment where either is attributed to the high AP). If a decision is made to treat a cat with what is judged to be a hypertensive crisis, therapeutic intervention will generally be with a parenteral agent, such as 0.2 mg/kg hydralazine IV or IM, repeated q2h as needed, or an oral calcium channel blocker (CCB) (Table 35-6). If parenteral medications are used, frequent repeated (at least every 30 minutes) AP monitoring is recommended. As an alternative, many veterinarians prefer oral CCBs (e.g., 0.25 to 0.5 mg amlodipine, PO, every 24 hours) because they generally decrease AP regardless of the underlying primary

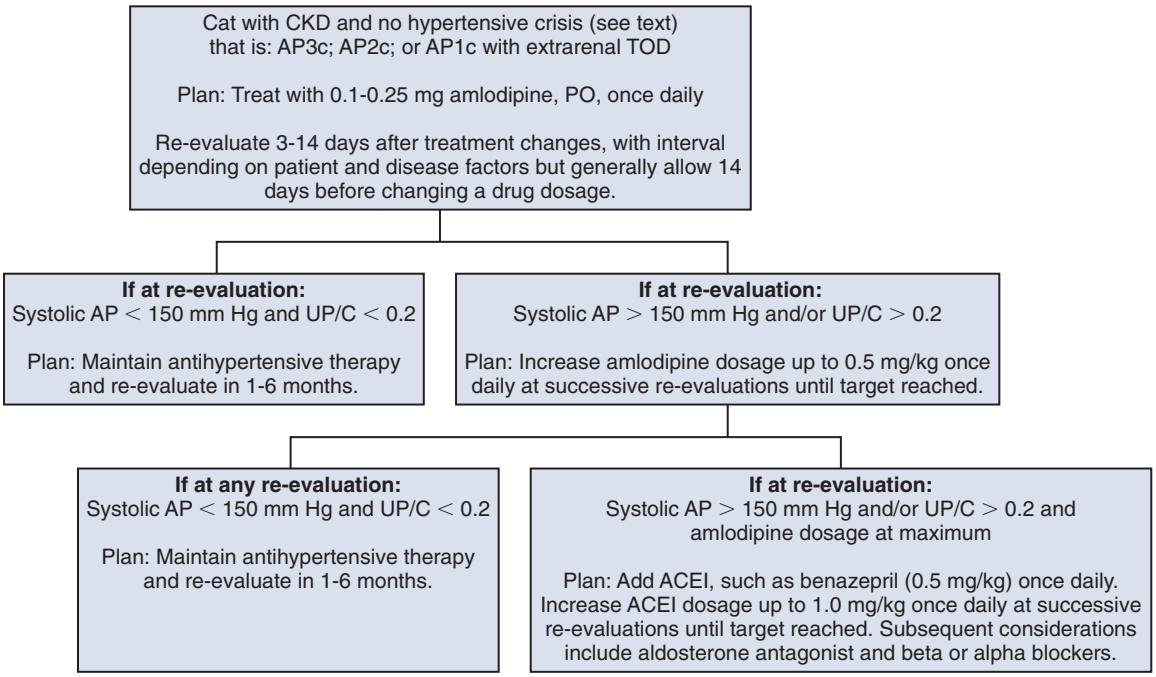

FIGURE 35-3 Approach to treatment of concurrent chronic kidney disease (CKD) and hypertension.

disease. Amlodipine generally reduces BP by 25 to 50 mm Hg in hypertensive cats within 4 hours of oral administration and poses limited risk of causing hypotension. If an oral CCB is used, it may be appropriate to send the animal home to reduce the stress associated with hospitalization and re-evaluate AP and TOD in 24 to 72 hours.

CHRONIC THERAPY: DOSAGES AND MONITORING

Decisions to use antihypertensive drugs should be based on integration of all clinically available information; a decision to treat, which may effectively mandate lifelong drug therapy, warrants periodic, judicious re-evaluation. Antihypertensive therapy must be individualized to the patient and its concurrent conditions. Regardless of the initial level of AP, the ideal goal of therapy should be to maximally reduce the risk of TOD, which generally means stage AP0 (systolic AP < 150 and diastolic AP < 95 mm Hg) and UP/C less than 0.2. Often, a more realistic goal of therapy is to achieve a UP/C less than 0.4 and a reduction by at least one AP stage, which generally equates to a drop in AP greater than 20 mm Hg. Except in hypertensive crises (see above), this can be achieved with a gradual, persistent reduction of AP. Although frequently recommended as an initial step in the management of high AP, restriction of dietary salt is controversial,[35,134] and available evidence suggests significant sodium restriction alone generally does not reduce AP and in fact, in dogs, activates the RAAA with a resulting elevation of AP in certain settings.[84,96] On the other hand, high salt intake may produce adverse consequences,[134] particularly in animals with chronic kidney disease. Until more data are available, the selection of appropriate diet should be based on other patient-specific factors, such as underlying or concurrent diseases and palatability.

In cats with CKD and either an AP in the moderate- or high-risk substage (AP2 and AP3; see Table 35-4) or extrarenal TOD (e.g., hypertensive retinopathy) in substage AP1, antihypertensive therapy is appropriate (Figure 35-3). Once a decision is made to treat a cat with high AP, therapeutic intervention will almost always include a pharmacologic agent.

IMPORTANCE OF SUSTAINING RENAL FUNCTION DURING ANTIHYPERTENSIVE THERAPY

In human beings with essential hypertension, azotemia is absent and diuretics and beta blockers are commonly used as first-line therapy. However, these agents can produce dehydration (diuretics) and activate the renin-angiotensin-aldosterone system (diuretics and beta blockers), which is undesirable in cats with CKD. As a result, antihypertensives whose mode of action is vasodilation are most commonly used in hypertensive cats with CKD. These agents include CCBs and angiotensin-converting enzyme inhibitors (ACEIs), because they

tend to sustain renal function while reducing AP and UP/C (see Table 35-6 and Figure 35-3). There has been some concern about acute exacerbation of azotemia with ACEIs, though this is an unusual complication, and modest increases in serum creatinine concentration (<0.5 mg/dL [44.2 µmol/L]) may occur and are generally tolerable.

The ACEIs and CCBs are the most widely used antihypertensive agents in cats. Because of their dramatic antihypertensive efficacy, CCBs, specifically amlodipine, are the treatment of first choice with a starting dose in the lower half of the recommended range (see Table 35-6). Often a 2.5-mg (or 5-mg) tablet is carefully halved or quartered for dosing. This medication may be compounded by a pharmacist to permit more precise dosing.

A patient should be evaluated 3 to 14 days following the institution of antihypertensive therapy and at a similar time after any dosage adjustments. In unstable patients and those with IRIS stage IV CKD, this recheck should be conducted in a shorter time frame, perhaps 3 to 7 days. Patients deemed to be hypertensive emergencies (see above) and hospitalized patients, particularly those receiving fluid therapy or pharmacologic agents with cardiovascular effects, should be assessed daily. The purpose of these short-term assessments is to determine if there are any unexpected (e.g., new or worsening TOD) or adverse findings (e.g., marked worsening of azotemia or development of systemic hypotension). An AP less than 120/60 mm Hg combined with clinical findings of weakness, syncope, and/or marked tachycardia indicates systemic hypotension, and therapy should be adjusted accordingly.

The ideal target is to adjust therapy to achieve an AP with minimal risk of further TOD (i.e., systolic AP < 150 mm Hg) and to eliminate proteinuria (i.e., UP/C < 0.2). In most hypertensive cats with CKD, treatment with a CCB alone or with a CCB plus an ACEI will provide acceptable control of AP and proteinuria. It will be impossible to achieve both targets in many patients, making it important to individualize care using clinical judgment. If adequate antihypertensive effect is observed and the patient remains stable, subsequent re-evaluation may be performed 3 to 6 weeks later. If additional lowering of AP is desired, the CCB dose may be increased (generally by doubling dosage up to the maximum dosage of 0.5 mg/kg, PO, every 24 hours). Amlodipine has a 30-hour duration of effect on AP in cats; so, twice daily dosing is not helpful. If a patient remains proteinuric and/or hypertensive on a CCB, the addition of an ACEI without lowering the CCB dosage is appropriate. If the combination of a CCB plus an ACEI is incompletely effective, an aldosterone antagonist (e.g., spironolactone) or a beta blocker (e.g., atenolol) may be added. The former is of theoretical value, since cats with CKD seem to be prone to hyperaldosteronism. Atenolol or another beta blocker may be more efficacious as supplemental therapy in cats with CKD, hypertension, and hyperthyroidism. Other considerations for poorly responsive cases include oral hydralazine and alpha blockers.

ADDITIONAL PATIENT EVALUATIONS

Scheduled evaluations of hypertensive cats with CKD should include a thorough history and physical examination, complete serum biochemical panel, hematology, urinalysis, assessment of UP/C and AP, ophthalmic examination, and aerobic bacterial urine culture. Evaluations should be done every 1 to 4 months in cats with poorly controlled AP and UP/C. If AP and UP/C are stable and controlled, approximate intervisit intervals would be

- IRIS stages I and II: 6 months
- IRIS stage III: 3 to 4 months
- IRIS stage IV: 1 to 2 months

As noted above, cats with concurrent CKD and hypertension with unstable renal function, extrarenal complications of hypertension, or cats that are undergoing adjustments to therapy should also be seen more frequently, often every 3 to 14 days.

CONCLUSION

The proper management of a cat with concurrent CKD and systemic hypertension requires a clear understanding of the interaction between these two entities, an appreciation of the role of judicious use of antihypertensive agents, and frequent re-evaluations of AP, UP/C, and serum creatinine.

IMMUNE DEFICIENCY, STRESS, AND INFECTION

Lisa M. Singer and Leah A. Cohn

IMMUNODEFICIENCY

A cat is protected from potential pathogens by physical (e.g., epithelial surfaces) and mechanical (e.g., cough reflex) barriers as well as the innate and adaptive immune responses. Generic responses to potential pathogens form the innate immune system. These responses include phagocytosis, attack by natural killer cells, and complement-mediated destruction, among others. For those pathogens that evade physical barriers and innate responses, a more specific, targeted set of responses is evoked. These adaptive responses are particular to a

given pathogen, and once they have been stimulated, memory of that response is retained such that subsequent responses to that pathogen are improved in quantity and quality. Both cell-mediated immunity (CMI) and humoral immunity are branches of this adaptive immune response. Both intimately involve the actions of lymphocytes and are guided in part by helper T-lymphocytes (CD4+). In CMI, pathogens are destroyed largely through the actions of cytotoxic T lymphocytes (CD8+), while humoral immunity relies on antibody secreted from activated B lymphocytes (i.e., plasma cells).

Immunodeficiency occurs when one or more components of the immune system are compromised, and cats suffering from immunodeficiency are said to be immunocompromised. These cats are more susceptible to infection than healthy cats, and established infections can be a challenge to cure. In addition, some immunodeficiencies of the adaptive immune system predispose the patient to cancer, especially lymphoproliferative and skin cancers.[50,94,215] Primary immunodeficiency results from an inherited or congenital defect in innate, CMI, and/or humoral immunity. Secondary immunodeficiency occurs when acquired disease or therapy damages immune protections. Although the immune system offers redundant and overlapping protective mechanisms, innate phagocytic, CMI, and humoral immunity are each particularly adept at providing protection from certain types of pathogens (Figure 35-4).

Primary hereditary immunodeficiencies are extremely rare in cats. They are suspected when several related kittens die in utero, fail to thrive after birth, or succumb to early infection. Other clues to the presence of primary immunodeficiency are persistent or recurrent infections in young animals, atypical infections, failure to respond to vaccination, hypoglobulinemia, persistent leukopenia, or morphologic abnormalities in white blood cells. Some hereditary abnormalities of the immune system are benign, while others increase susceptibility to infection to varying degrees. Only a handful of primary immunodeficiencies are recognized in cats (Table 35-7), but it is quite likely that additional abnormalities are as yet unrecognized.

The vast majority of immunocompromised cats have an acquired immunodeficiency state. The causes are varied (Box 35-3) and may impact a single aspect of immunity (e.g., immune mediated neutropenia affects only innate phagocytic immunity) or several components of immunity (e.g., malnutrition affects innate, CMI, and humoral immunity).[132] Some causes of acquired immunodeficiency are reversible, for instance, withdrawal of immunosuppressive drug therapy. Others can be addressed directly, for instance, administration of plasma to kittens with failure of passive transfer.[151] Unfortunately, for many causes of immunodeficiency,

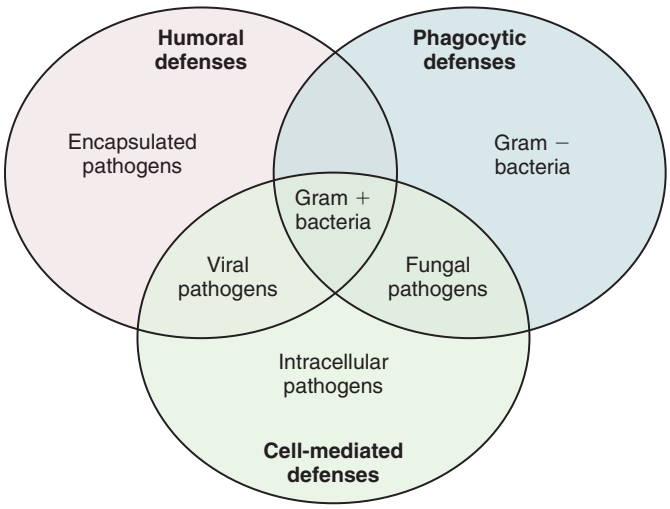

FIGURE 35-4 Although protections from various aspects of the immune system are redundant and overlapping, each is particularly adept at providing protection from certain types of insult. The types of infections that occur offer clues to the type of immunodeficiency present. For instance, defects of phagocytic immunity leave the host particularly susceptible to bacterial and fungal infections without much impact on susceptibility to viral infection.

TABLE 35-7 Primary Immunodeficiency Syndromes of Cats

Immunodeficiency	Defect	Effect	Diagnosis
Pelger-Huet anomaly (various cat breeds)[49,145]	Granulocyte nuclear hyposegmentation	Little if any impact on disease susceptibility	Morphologic examination of stained blood smears
Chediak-Higashi Syndrome (blue smoke Persians)[139]	Impaired phagocyte, platelet, and melanin granule membrane fusion	Minimal compromise of innate phagocytic immunity; color dilution; bleeding caused by defective platelet granules	Morphologic examination of stained blood smears
Neutrophil granule anomaly (Birman cats)[102]	Eosinophilic granules in the cytoplasm of neutrophils	Little if any impact on disease susceptibility	Morphologic exam of stained blood smears
Hypotrichosis with thymic atrophy (Birman cats)[40]	Kittens are born hairless and without a thymus, the site of T-lymphocyte development	Stillbirth, early euthanasia, or death because of infections in first 3 months	Suspected in hairless Birman kittens; thoracic imaging; lymphocyte blastogenesis; necropsy

BOX 35-3
Causes of Secondary Immunodeficiency in Cats

- **Infectious disease**
  Feline leukemia virus
  Feline immunodeficiency virus
  Panleukopenia
- **Endocrinopathy**
  Diabetes mellitus
  Hyperadrenocorticism
- **Neoplastic disease**
  Lymphoma
  Leukemia
  Multiple myeloma
- **Immune-mediated disease**
  Immune-mediated neutropenia
- **Metabolic disease**
  Renal failure
  Hepatic failure
  Malnutrition
- **Iatrogenic**
  Splenectomy
  Chemotherapy
  Whole body radiation
  Glucocorticoids
  Cyclosporine
- **Miscellaneous**
  Failure of passive transfer
  Extremes of age
  Pregnancy
  Neutropenia of any cause
  Stress?

while the secondary infections can be treated, the underlying immunodeficiency state cannot be corrected.

The most common causes of immunodeficiency in cats are infection with the retroviruses: feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV). Cats infected with FeLV may develop blood dyscrasias or neoplasia, but often succumb to secondary infections within 1 to 3 years of diagnosis. Cats with FIV infection have a more protracted course and often live for many years before developing complications such as secondary infection. Both viruses affect several aspects of immune responsiveness but are especially damaging to CMI.[117,150,251] Both the American Association of Feline Practitioners and the European Advisory Board on Cat Diseases have recently developed documents that review the pathophysiology, epidemiology, diagnosis, and treatment of cats with retroviral infection.[117,150,152]

Although antiviral drugs have dramatically altered the outcome of retroviral immunodeficiency in people, toxicity and costs make these drugs less useful in cats, and to date, there is no published evidence that antiviral drugs reduce the incidence of secondary infection in this species. Only a few studies have evaluated the potential benefit of immunomodulatory drugs in cats with retroviral infection, with little benefit demonstrated in the way of efficacy.[117,150,152,160] A study of recombinant feline interferon omega suggested an improved survival, but further studies are clearly warranted.[53,92] A new product, Lymphocyte T-Cell Immunomodulator (LTCI; Imulan BioTherapeutics, Prescott, Ariz.), has recently gained conditional approval by the United States Department of Agriculture (USDA) as a treatment aid for FeLV- or FIV-infected cats with opportunistic infection and other retroviral complications. No peer reviewed, controlled studies demonstrating efficacy of this protein in recovery from secondary infection or improved survival in retroviral infected cats have been published to date.

STRESS AND DISEASE

In the 1930s, the endocrinologist Hans Selye coined the term "stress." He postulated that a stressor stimulus could result in a state of stress wherein an organism would respond in a physiologically inappropriate way that could contribute to the development of disease.[207] The stressor could be either physical (e.g., thermal) or psychological (e.g., fear) and could be either real or perceived. In cats, the introduction of a new pet or family member, changes in the familiar environment (e.g., moving to a new home, an outdoor cat becoming an indoor cat, changes in litter box management), changes in food or feeding, and many other seemingly innocuous stimuli might act as stressors. Acute and chronic stress invoke different chemical mediators and different physical effects. Acute stress results in excessive production of sympathetic hormones, such as norepinephrine, while chronic stress results in stimulation of the hypothalamic-pituitary-adrenal axis and excessive cortisol production. Biological stress can have profound effects on not only the nervous and endocrine systems but on the immune systems as well, and stress can play a role in increased susceptibility to infection as well as provoking other physical and behavioral aberrations.[37,43,162,203]

Chronic stress is believed to result in an increased susceptibility to infection, perhaps in part as a result of cortisol excess.[36,200] Unfortunately, the specific effects that stress has on susceptibility to infection are difficult to evaluate except in very homogenous experimental settings. For instance, the prevalence of feline herpes virus (FHV-1) viral shedding in apparently healthy cats surrendered to a shelter for adoption was only 4%, but after 1 week in the stressful shelter environment, 52% of cats were shedding FHV-1.[177] It is essentially impossible to determine if this increase is due to stress-related acquisition of new infection, stress-related recrudescence of latent infections, simple proximity to infected cats, poor sanitation or air quality, or a combination of these and other factors. Exogenous corticosteroids can increase the

rate of shedding of FHV-1, and endogenous corticosteroid release is an important component of chronic stress.[99] No treatment to date, including L-lysine, has been found to reduce the rate of FHV-1 shedding in stressed cats.[62]

The role of stress in other disease states, especially interstitial cystitis, is under investigation in cats. Lower urinary tract signs unassociated with urinary infection, urolithiasis, or neoplasia are common in cats. Often identified as interstitial cystitis (IC) or idiopathic feline lower urinary tract disease, this condition has recently been postulated to have a neuroendocrine basis.[28,243,246,248] The psychological stress associated with an indoor-only environment may help account for the increased risk of IC in indoor cats.[30] If IC is largely caused by stress, the ideal treatment is to reduce stress. This includes measures aimed at enriching the environment of the indoor cat; such multimodal environmental modifications are described in the literature and are accessible to veterinarians and owners alike via the Internet (The Indoor Pet Initiative; http://indoorpet.osu.edu).[29] When stress cannot be eliminated, drugs with sympatholytic activity, such as amitriptyline, have been used to treat IC in cats, but these drugs can have serious adverse effects in some cats.[44]

MANAGEMENT OF THE IMMUNOCOMPROMISED CAT

Cats with immunocompromise and no symptomatic infection nonetheless require special considerations, which vary with the cause and type of immunodeficiency. The most common examples include "healthy" cats with retroviral infection or cats receiving immunosuppressive drug therapy. Ideally, immunocompromised cats should be housed indoors-only, and new pets should be introduced to the home only after a complete health screening of both pets. Raw meat diets should be avoided because of the risk of salmonellosis. Ideally, cats with chronic immunocompromise should be examined twice yearly, paying particular attention to oral and ocular evaluation. Veterinarians should address both ectoparasite and endoparasite control.

Depending on the type and severity of immunocompromise, even cats with abnormalities of the adaptive immune system can often mount an effective vaccination response. Therefore these cats should receive vaccinations; however, modified live vaccines are best avoided when adaptive immunity is compromised. Twice yearly screening with CBC, serum biochemistries, and urinalysis are suggested. Owners of immunocompromised cats must be instructed that even seemingly mild illness should prompt veterinary care, because early recognition of infection and appropriate treatment can be life saving. Prophylactic antimicrobial therapy is not indicated in healthy cats with immunocompromise, except prior to dental procedures or in the face of severe ($<1{,}000 \times 10^3/\mu l$) neutropenia. The role for immunostimulatory drugs (e.g., feline interferon omega, acemannan, granulocyte colony-stimulating factor [G-CSF], *Staphylococcus* protein A) has yet to be defined for most causes of immunodeficiency in cats.[117,150,152,160]

Opportunistic infections are important in animals with immunocompromise. These infections are not always readily apparent, since the clinical signs of infection may be similar to the signs of the underlying cause of immunodeficiency, or because the cause of immunodeficiency may mask clinical signs of infection (e.g., glucocorticoids suppress fever). Although there are a myriad of potential opportunistic pathogens, a few warrant mention. Demodicosis can occur in any cat, but it seems to be a greater problem in cats with immunodeficiency associated with conditions such as FeLV, FIV (see Figure 33-21), diabetes mellitus, and neoplasia.[169] Candidiasis, a major problem in immunocompromised people, is very rare in healthy cats. However, urinary, ocular, and systemic candidiasis has been identified in immunocompromised cats.[76,188] The vast majority of cats infected with *Toxoplasma gondii* remain healthy; cats that develop an immunodeficiency disease or undergo iatrogenic immunosuppression are more likely to develop clinical illness as a result of previously subclinical infection.[8,14,51,76] Immunosuppressive drug therapy has been associated with feline mycobacteriosis.[87,119,163] Retroviral infections are risk factors for several other types of infections, including *Cryptococcus neoformans*, *Mycoplasma haemofelis*, feline infectious peritonitis, and coccidiosis, among others.[9,98,122,220] Immunodeficiency apparently does not increase the risk of feline bartonellosis, but may increase pathogenicity.[19,77]

Active infection in immunocompromised cats requires aggressive treatment. Outpatient treatment reduces the potential for nosocomial infection. If hospitalization is necessary, caretakers should wash their hands before and after handling the cat and should wear gloves. If feasible, the cat should be isolated from other animals and especially other cats. Aseptic technique should be used whenever protective barriers are disrupted (e.g., catheter placement).

Aggressive antimicrobial treatment of infections can be life saving in immunocompromised cats, and even cats with chronic immunosuppressive conditions may be cured of secondary infections. Because bacteriostatic antimicrobials slow bacterial growth but rely on a functional immune system to clear an infection, bactericidal drugs should be used in immunocompromised cats. Empiric antimicrobial choices are best guided by the source, site, and likely pathogens involved in infection, along with cytology and Gram stain results from the infected site. Antimicrobial therapy is instituted pending culture results, but appropriate samples (e.g., cavity

effusions, blood, urine,) should be collected. When sepsis is suspected, the ideal is to collect three blood cultures of 10-mL volume but this volume is excessive for many cats.[146] Even in healthy cats, no more than 10 mL/kg of blood should be collected.[120] Cats with severe illness are often anemic and dehydrated, and blood is usually also collected for CBC, serum chemistries, and other diagnostic tests. When the volume of blood for culture is limited, the authors prefer to collect two cultures each with at least 7-mL volume as opposed to more cultures with lower volumes.

Fever in an immunocompromised cat, especially with neutropenia or neutrophilia, is a medical emergency. Bacteremia or sepsis occurs more often in patients with an impaired immune system but can be difficult to recognize in cats.[61] Although hyperglycemia is common in cats with sepsis, this finding is common in cats with many types of illness or stress and thus cannot be relied on as a sign of sepsis.[42,86] When sepsis is suspected, broad-spectrum, parenteral antibiotics are recommended (e.g., a combination of a beta lactam plus either an aminoglycoside or fluoroquinolone; use caution: enrofloxacin can cause blindness at doses exceeding 5 mg/kg/day). If there is no clinical improvement after 48 hours of empiric therapy, a change in antimicrobial agents should be considered. Treatment is continued for at least 1 week beyond resolution of clinical signs.

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