HEPATIC LIPIDOSIS – MANAGING & FEEDING THE ANORECTIC CAT  
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Introduction
Hepatic lipidosis (HL) is a common sequel to inappetence in cats regardless of the cause of appetite disruption. It is the most common form of liver disease diagnosed in cats in North America. Treating the caloric deficiency must be the first priority. Diagnostics are required to define the underlying cause(s) to enable treatment and correction of the same where feasible. When cytology is utilized, it is important to interpret findings in light of collection method. Aspiration will result in lipid being harvested in any inappetant cat, regardless of cause; passive fine needle biopsy provides a greater opportunity to evaluate cells in the liver.

Successful therapy of lipidosis requires aggressive nutritional support feeding adequate amounts of a balanced diet to reverse the catabolic state. Good quality, biologically available protein is necessary and this nutrient should not be restricted unless a patient is showing evidence of hepatic encephalopathy. Early treatment with Vitamin K1 allows fine needle or exploratory biopsy as well as large bore tube placement, which is key to recovery. Fluid therapy for tissue perfusion, oxygen delivery, waste scavenging and the correction of electrolyte imbalance, especially hypokalemia, is essential. Addressing concurrent or underlying problems that have contributed to the inappetence is very important. Drugs used in the treatment of feline lipidosis include antiemetics if needed, taurine, arginine, S-adenosyl-L-methionine, L-carnitine, ursodeoxycholic acid, silibinin and Vitamins B and K1.

Etiology And Pathophysiology
Anything causing a significant decrease in dietary intake or cellular starvation can result in lipidosis in cats. Thus, uncontrolled diabetic cats often have concurrent lipidosis despite polyphagia. It is unlikely that one pathogenesis explains HL in all affected individuals, however alterations in fat metabolism are key.

There are five types of fat in the liver: triglycerides (TG), phospholipids, lipoproteins, cholesterol and cholesterol esters. Lipid vacuolation in lipidosis is predominantly composed of triglycerides. They accumulate in the liver when the rate of hepatic synthesis exceeds their dispersal. Hepatic TGs are produced from fatty acids from systemic circulation (dietary lipids and adipose stores) and from de novo synthesis within the liver. Over nutrition with carbohydrates or protein results in hepatic fat accumulation, as these excess nutrients are stored as triglycerides.

Systemically ill cats generally develop some degree of hepatocellular fatty vacuolation despite an increased rate of very low-density lipoprotein (VLDL) secretion. A 2004 study (Blanchard) showed that TG, VLDL, low density lipoprotein (LDL) and high density lipoprotein (HDL) levels are all increased in cats with lipidosis suggesting that VLDL secretion is enhanced, VLDL and LDL catabolism is reduced and lipoprotein exchange is impaired.

Fatty vacuolation is not problematic until the degree of vacuolation is morphologically severe. In a normal feline liver, neutral fat comprises < 5% of total organ weight. In contrast, the liver of a cat with HL may double or triple in weight due to fat accumulation. Over-nutrition augments hepatic fat accumulation; feeding a high proportion of dietary carbohydrates may have an
inhibitory influence on mitochondrial fat oxidation favouring hepatic fat accumulation. Feline obesity predisposes to development of HL: in inappetant obese cats, release of fatty acids from their ample peripheral adipose stores challenges the liver’s capacity for fat utilization and dispersal.

The metabolic balance of lipolysis and storage of TGs is influenced by blood glucose concentrations as well as diverse hormonal and neural mechanisms. Hormone sensitive lipase (HSL, promoting adipocyte lipolysis) and lipoprotein lipase (LPL, promoting fat uptake into adipocytes) directly influence adipocyte fat metabolism. Adipocyte LPL activity promotes fat uptake in the well-fed individual. In starvation, LPL activity declines, while that of HSL increases. Thus, lipolysis exceeds fat uptake. A previously obese individual undergoing starvation is at increased risk for lipolysis.

Norepinephrine, epinephrine, growth hormone, glucagon, corticosteroids, and thyroxin increase HSL activity, whereas insulin inhibits it. Since this effect is enhanced in the absence of insulin, occult or overt hepatic TG accumulation in unregulated diabetics is common. While LPL promotes fat uptake into adipocytes in the well-fed condition, during starvation, LPL activity declines and HSL increases creating a hormonal balance favouring hepatocellular fat accumulation. Therefore, an obese individual undergoing starvation (anorexia) has increased risk for peripheral fat mobilization and excessive hepatic TG retention. Catecholamine release associated with stress or illness may result in NEFA release contributing to the development of lipidosis. (Brown)

Fatty acids may undergo beta-oxidation, be used for TG synthesis, be converted to phospholipids, be used in the formation of cholesterol esters, or be packaged with apoproteins for dispersal as lipoproteins. The most important route for TG dispersal is via formation of VLDL. This requires intact lipid transport through subcellular compartments, particle combination with apoprotein, formation of a secretory particle and a vesicle and out of the hepatocyte and into the perisinusoidal space. Impairment at any one of these steps will prevent mobilization of hepatic fat. An imbalance between essential lipoprotein components will also interfere with fat dispersal. Brown et al showed that cats with HL have a higher concentration of nonesterified fatty acids (NEFA) compared to cats with cholangiohepatitis suggesting that hormone sensitive lipase is unimpaired. Catecholamines associated with stress or illness may result in NEFA release (as well as HSL) contributing to the development of lipidosis.

In 2013, Mazaki-Tovi reported that adiponectin levels are elevated in cats with lipidosis or other liver disease, increased concentration of leptin was found only in cats with HL. Adiponectin concentrations correlated with ALT activity whereas leptin levels correlated with alkaline phosphatase activity.

The essential interaction of fatty acids and L-carnitine at mitochondrial membranes influences both the intraorganelle activation of fatty acids and their availability for beta-oxidation. Carnitine may improve fatty acid oxidation but not in a cat being fed a diet low in n-3 fatty acids (Ibrahim). In addition, dietary L-carnitine appears to protect against ketosis during weight gain (Blanchard, 2002).
Deficiency of hepatocellular GSH in cats with HL may reflect intramitochondrial GSH insufficiency where it is needed for redox-balance to sustain continued energy production. Finding hepatic GSH deficiency in cats with HL implicates dysfunction of the transsulfuration pathway with diminished SAMe availability. Low GSH levels are common in liver disease in cats (Center 2002)

**Clinical Findings And Diagnostics**

Cats of any age may be affected by HL. Domestic shorthair cats are commonly affected but this may reflect breed popularity. Obese middle-aged females are most often reported, but any inappetant cat may develop lipidosis. The period of inappetence or anorexia may be as short as 2 to 7 days. Initial clinical features include inappetence, weight loss, vomiting, lethargy, diarrhea or constipation and weakness. Unless hepatic encephalopathy is present (rare), cats generally remain bright and alert. Physical findings include dehydration, variable icterus, an unkempt appearance, and palpable liver margins. Although fat may become depleted on the limbs and dorsal trunk, abdominal fat stores are preserved. Rarely, skin fragility has been reported (Trotman, Daniel).

Hematologic features include a nonregenerative anemia and a stress leukogram reflecting the primary illness causing anorexia. Poikilocytosis is common and may reflect altered RBC membrane lipids, metabolism or oxidative stress affecting cell membrane flexibility. Biochemical changes reflect cholestasis, and to a lesser degree, altered hepatocellular membrane permeability and viability. Most cats have a markedly increased ALP activity with lesser magnitudes of increase in transaminases. Occasionally, a cat will have high transaminases with only modest ALP activity. Finding high GGT activity in a cat with HL increases suspicion of underlying pancreatitis, pancreatic neoplasia, cholangiohepatitis, major bile duct obstruction, cholelithiasis or choledochitis, or biliary tree neoplasia. Hyperbilirubinemia and high serum bile acid concentrations are common. Hypokalemia reflects inappetence and is significantly associated with failure to survive if uncorrected. Hypochloremia may reflect vomiting. Hypophosphatemia reflects intercompartmental shifts in phosphate and most commonly heralds onset of a refeeding syndrome. Urinalysis typically reports urobilinogen with bilirubin pigmenturia and bile crystalluria.

Because most cases of lipidosis are secondary to something causing inappetence, ultrasound is helpful to look for the underlying problem. Evaluate the liver, pancreas, stomach, small and large bowel to determine if there is triaditis (inflammation of the liver, pancreas and bowel), disease of the gall bladder and biliary tree, etc. In one study, 38% of cats with HL had concurrent histopathologic acute pancreatitis and the recovery rate of cats with acute necrotizing pancreatitis plus lipidosis was 20% rather than >80% of cats with HL alone.

Ultrasonographically, the liver characteristically shows a hyperechoic parenchyma, however, in a recent report, it was concluded that statistical evaluation of ultrasonographic criteria did not yield clinically acceptable accuracy for discrimination among the 7 categories of diffuse liver diseases (including normal liver) in either cats or dogs. Liver aspirates demonstrate profound, but nonspecific, hepatocellular lipid vacuolation with more than 80% of hepatocytes markedly affected. Aspiration cytology is adequate for a presumptive diagnosis of HL, hepatic lymphoma, and overt hepatic sepsis but is unreliable for detection of necroinflammatory disorders as they
cannot rule out, or definitively confirm, cholangitis or cholangiohepatitis. Harvesting cored samples using a passive collection, rather than active aspiration, may improve the yield of the samples.

Surgical or laparoscopic biopsy of the liver is usually not necessary and purposely avoided to minimize anaesthetic and hemorrhagic complications. However, if other organs are affected, surgery should be considered to get multiple organ biopsies (and to place a g- or e-tube) if the patient is stable enough and once coagulation factors and electrolyte abnormalities are corrected. On gross inspection, the liver is yellow-tan in colour, tissues are friable, and biopsy specimens float in formalin. Histopathology of hepatic biopsies reveals profound hepatocellular vacuolation. However, lipid globules can only be confirmed on frozen sections stained with oil red O; paraffin embedment of tissue results in lipid extraction.

**Therapy**
The **most important** treatment is provision of a balanced, not protein-restricted feline diet delivering adequate energy (goal feeding of 40-60 kcal/kg ideal weight/day). Lack of nutrients promotes lipolysis and glycogenolysis. This fuels the already imbalanced TG dispersal mechanisms. Protein is essential for this process, in order to make lipoproteins VLDL, thus protein restriction is contraindicated unless encephalopathy (HE) is present. Dietary management of IHL cats should consist of a higher protein, lower carbohydrate diet. Arginine is needed for normal detoxification of nitrogen. Cage resting cats with HL may reduce muscle release of ammonia, thus may be beneficial.

Protein should only be restricted in patients with irrefutable signs of hepatic encephalopathy in order to reduce the production of false neurotransmitters. Carbohydrates as a source of calories are problematic as these cats are already prone to insulin resistance. If HE is present, then lactulose (0.25-2 ml/kg to effecting soft stools), plus metronidazole (7.5 mg/kg PO q12h) are indicated.

**Feeding** is best achieved using a large bore feeding tube to avoid development of food aversion that may follow forced oral alimentation. Use of large bore tubes is associated with improved survival. Esophagostomy tubes are preferred as these are placed quickly and have fewer complications than gastrostomy tubes. However, initial feeding may be via a nasoesophageal tube while correcting of hydration and initial electrolyte abnormalities. The large bore tube may be placed once the patient is stable enough to tolerate anaesthesia and bleeding tendencies have been circumvented by administration of vitamin K₁. The number of feedings per day is determined based on the volume of food tolerated per feeding. Carbohydrate supplementation is not advised (e.g., dextrose infusion) because of its inhibitory influence on fatty acid oxidation.

Appetite stimulants including cyproheptadine (1 mg/cat PO BID), mirtazapine (2-3 mg/cat PO q72h) may help jump-start a cat’s appetite, but one must be wary not to lose sight of total calories consumed. If a cat is eating but not enough, supportive feeding (assisted syringe feeding or tube feeding) must be considered. A cat eating small amounts of baby food will not meet his caloric needs until he eats two – three jars/day. Meat baby food is not balanced, but is sufficient for several weeks. There are several diets specifically designed for the assisted feeding of cats (Royal Canin Recovery, Hill’s a/d, Eukanuba Maximum Calorie), liquid balanced enteral diets
for cats (Clinicare, Rebound) Additionally, we can make a slurry from any canned food. In order to minimize loss of caloric density, blend with one of the liquid diets rather than water.

There are numerous options for assisted feeding. In general, this author starts with syringe assisted feeding until the cat is stable enough to allow the brief anaesthetic required for the placement of an esophageal tube. Because liver disease is known to be present, three doses of Vitamin K1 are given SC (1.0 mg/kg q12h SC) prior to tube placement, biopsies or any other procedure that might result in bleeding.

Placement of esophageal tubes is discussed elsewhere. Suffice it to say that the instrumentation for this procedure is very basic requiring only the following: 14-16 Fr red rubber feeding tube/urinary catheter, Carmalt or other long curved forceps, a scalpel blade, suture and bandaging materials and a multiple use injection port (prn adaptor). A brief anaesthetic is required. Several protocols are appropriate including propofol, despite hepatic metabolism, whose use did not increase morbidity or fatalities in cats with primary lipidosis.

Calculating how much to feed requires that you know the patient’s current weight as well as their healthy weight and the caloric densities (kcal/ml) of the diet you are intending to use (see Table 1). Use 50 kcal/kg as a rough guide to determine calories needed. Start by feeding 1/3-1/2 of the calories needed for the current, inappetant weight. On day two, feed 2/3-3/4 of this number and on day three, feed the full calories needed for the current weight. For weight gain, gradually increase to the calories needed for the cat’s healthy weight.

Example: 3.4 kg sick cat BCS 3/9, healthy weight 4.0 kg BCS 5/9
% weight change = (4 – 3.4) / 4 = 15%
4.0 kg X 50 kcal/kg/day = 200 kcal by day 3
200 kcal = 95 ml Iams Maximum Calorie
  OR 154 ml of Hill’s a/d or Royal Canin Recovery or PVD CN
Day 1 feed 35 ml of Max Cal or 50 ml of the other diets
Day 2 feed 70 ml of Max Cal or 100 ml of the other diets
Day 3 feed 95 ml Max Cal or 154 ml of the other diets.

With surgically placed tubes there is a delay in how quickly one can start to use them. The esophageal tube requires only a 2-3 hour delay to ensure full recovery from anaesthesia whereas gastrostomy and jejunostomy tubes require a longer wait of 10-12 hours. This is to ensure that some healing has begun to reduce the chance of food leaking from around the tube through the stoma into the peritoneal cavity. Any tube may clog. Should this occur, a cola-type soft drink, pancreatic enzymes or meat tenderizer can be instilled into the tube, left to incubate for about 10 minutes before attempting to flush tepid water through the tube to check for patency.

Cats can eat with any of these tubes in place. It is recommended to avoid offering food for a week to reduce the likelihood of them developing aversion to the food offered. Once a cat is eating well with tube in place the question becomes when one can remove the tube. Weigh the cat and, as long as he/she is eating well, avoid using the tube (for nutrients) for a week then reweigh the kitty. If the weight is stable (or increased), then it is safe to remove the tube. Because of stoma formation (except with nasoesophageal tubes), removal does not require
anaesthesia. Remove the suture (purse-string or stay sutures) and pull the tube out. In the case of a gastrostomy tube, straighten out the bulb/balloon by inserting a straight probe through the tube while concurrently pulling the tube out. Suturing is not required for any of the skin openings. Cleanse any minimal serous discharge that may occur for 2-3 days.

With the exception of nasoesophageal tubes, which should be only used short term (< 5 days), tubes may be left in place as long as a patient requires nutritional support. The longest that the author has had a gastrostomy tube in a cat was 18 months. If red rubber tubes are used rather than silicone or polyurethane, they may discolor and weaken over time. Esophageal tubes are easily changed. Simply remove the existing tube as described and, slip a new tube in through the stoma. A local anaesthetic will be needed to place a new purse-string suture. (Resource: Kitty Kollar e-tube collar: www.kittykollar.com)

How often should you feed? The number of feedings per day, (and hence timing), is determined based on the volume of food tolerated per feeding. Start with 6 ml and increase by 6 ml increments to about 36-48 for most cats. In the uncommon case of the patient who cannot tolerate even 6 ml boluses despite antiemetic therapy, trickle feeding may be instituted. Trickle feeding is a technique in which liquefied food is syringed into an empty fluid bag and administered gravitationally or by pump assistance via an intravenous line attached to the large bore feeding tube or by use of a large syringe filled with food and syringe pump. Care must be taken to renew food and delivery tubing and syringe at 12-hour intervals to avoid bacterial contamination. A promotility agent may be warranted.

<table>
<thead>
<tr>
<th>Table 1: Caloric densities, for feeding volume calculations</th>
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<tbody>
<tr>
<td>ReboundTM: 1 kcal/ml</td>
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<tr>
<td>ClinicareTM: 1 kcal/ml</td>
</tr>
<tr>
<td>Royal Canin/MediCal RecoveryTM: 1.23 kcal/ml</td>
</tr>
<tr>
<td>Hill’s a/dTM: 1.3 kcal/ml</td>
</tr>
<tr>
<td>Iams Maximum CalorieTM: 2.1 kcal/ml</td>
</tr>
<tr>
<td>PVD CNTM: 1.2 kcal/ml</td>
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</tbody>
</table>

**Vomiting** must be controlled. Although this can be achieved medically (see drug doses), it may also be alleviated by reducing meal volume, increasing the number of meals per day, using a trickle feeding approach with a syringe or fluid pump, and providing an opportunity for exercise (to stimulate enteric motility). Trickle feeding refers to placing liquefied food into an empty fluid bag and administering it gravitationally or by pump assistance via an intravenous line attached to the large bore feeding tube or by use of a large syringe filled with food and syringe pump. Care must be taken to renew food and delivery tubing and syringe at 8-hour intervals to avoid bacterial contamination. A promotility agent may be warranted as well.

<table>
<thead>
<tr>
<th>Table 2: Select Anti-emetics for use in the Cat</th>
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**Generic Name** | **Product™** | **Dose (feline)**
--- | --- | ---
Chlorpromazine | Thorazine, Largactil | 0.5 mg/kg q8h IM
Prochlorperazine | Compazine | 0.1 mg/kg q6h IM
Diphenhydramine | Benadryl | 2.0-4.0 mg/kg q8h PO
 |  | 2.0 mg/kg q8h IM
Dimenhydrinate | Dramamine, Gravol | 8.0 mg/kg q8h PO
Metoclopramide | Reglan | 1-2 mg/kg constant rate infusion IV over 24 hours
Ondansetron | Zofran | 0.1-0.15 mg/kg slow push IV q6-12 hours prn
Dolasetron | Anzemet | 0.6 mg/kg IV, SC q24h
Mirtazapine | Remeron | 3 mg PO q72h
Maropitant | Cerenia | 0.5-1 mg/kg SC, IV or PO q 24 hr

**Fluid support** is needed for rehydration as well as for maintenance of this state. It is best provided intravenously using non-lactate, non-glucose containing fluids. Lactate intolerance is suspected in HL and steady glucose infusion may potentiate hepatic TG accumulation. Dehydration impairs hepatic circulation, compromises normal detoxification processes, azotemia enhances ammonia production, and constipation augments absorption of colonic toxins. Aggressive attention to correction of hypokalemia is essential; hypokalemia is a negative predictor for survival. Use the customary sliding scale for fluid potassium supplementation. In the hypokalemic state, potassium (K) shifts from inside the cell to extracellular fluid. This parallels an increase in extracellular pH, which causes increases in intracellular ammonia trapping. In cats deficient in arginine, this becomes more severe. Hypokalemia also alters the threshold of response of neuroreceptors.

**Hypophosphatemia** may precede initiation of nutritional support but more commonly reflects a refeeding phenomenon within 12 hours of initial food ingestion. Hypophosphatemia is treated using potassium phosphate, delivered at 0.01-0.03 nmol/kg/hr. Monitor serum phosphate every 6 hours, and discontinue supplementation when serum phosphorus levels reach and sustain ≥ 2 mg/dL (≥ 0.65 mmol/L). Avoid iatrogenic hyperkalemia by adjusting KCl supplements to account for potassium delivered with the potassium phosphate. Water-soluble vitamins should be added to intravenous fluids (1 to 2 mL Vitamin B complex per litre of fluids). **Cobalamin** (Vitamin B₁₂) deficiency should be considered in HL cats with suspected intestinal or pancreatic disease. **Thiamine** (vitamin B₁) deficiency is also suspected in some cats with HL showing sluggish pupillary light responses, vestibular signs, and abnormal postural reactions, or severe neck ventroflexion. Because a vasovagal response may result from injected thiamine, the oral route is preferred (50 to 100 mg per cat per day for 1 week in those demonstrating consistent clinical signs).

Other differentials for neck ventroflexion in cats include hypophosphatemia, hypokalemia, hepatic encephalopathy, hyperthyroidism, neuromuscular weakness (e.g. myasthenia gravis), and disorders causing cervical vertebral or muscular pain.
Cats with HL are often deficient in vitamin K. Lack of dietary intake, altered intestinal bacterial flora subsequent to antimicrobial treatment, and impaired vitamin K epoxidase cycle associated with hepatic dysfunction are underlying causes. Treatment with vitamin K is recommended (0.5-1.5 mg/kg SC at 12-hour intervals X 3 doses). Vitamin K treatment must precede insertion of feeding appliances, jugular venipuncture, cystocentesis, hepatic aspiration, or hepatic biopsy.

Supplementation with 250 to 500 mg L-carnitine per day has been recommended yet there is no conclusive evidence that outcome is improved through using it. L-carnitine is an essential cofactor for fatty acid oxidation; supplementation may assist in preventing hepatocellular accumulation of free fatty acids and help remove toxic acetyl groups from the mitochondria. It is surmised that in HL a “relative” hepatocellular carnitine deficiency exists despite plasma or muscle carnitine concentrations. Owing to solubility issues, only medical grade liquid carnitine should be used.

Taurine supplementation is also recommended (250 to 500 mg/day), as this essential amino acid is obligatory for bile acid conjugation in the cat and cats with HL waste taurine in their urine. Taurine supplementation increases water solubility of bile acids, reduces their cellular toxicity, and facilitates their circulation and renal elimination. Because bile cannaliculi are narrowed, consider using ursodeoxycholic acid. This bile acid has a number of hepatoprotective effects and provides IgA to proximal duodenum. It requires taurine for conjugation.

S-adenosyl-L-methionine (SAMe) is a naturally occurring substance in the body. It initiates transmethylation, transsulfuration and aminopropylation. The first pathway contributes to cell membrane fluidity and carnitine synthesis among other actions. Transsulfuration is the process by which glutathione (GSH) is produced; glutathione is an important component of the antioxidant defence system detoxifying xenobiotics and protecting against oxidative injury. Via aminopropylation, SAMe may have anti-inflammatory and analgesic properties as well as assist in protein synthesis. All of these actions could be beneficial in supporting resolution of lipidosis. Nevertheless, no studies have been done to date that look at whether incorporation of SAMe improves response to therapy in cats with hepatic lipidosis. Cats with lipidosis or necroinflammatory liver diseases have been shown to have low liver tissue concentrations of glutathione.

Table 3: Drugs, Dosages and Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Frequency</th>
<th>Route</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>0.5 mg/kg</td>
<td>TID</td>
<td>IM</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Prochlorpromazine</td>
<td>0.1 mg/kg</td>
<td>QID</td>
<td>IM</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>8.0 mg/kg</td>
<td>TID</td>
<td>PO</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>1-2 mg/kg</td>
<td>Over 24 hours</td>
<td>CRI IV</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Ondansentron</td>
<td>0.1-0.15 mg/kg</td>
<td>Q6-12 h prn</td>
<td>Slow push IV</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose (mg/kg)</td>
<td>Administration</td>
<td>Route</td>
<td>Side Effect</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>----------------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>0.6</td>
<td>SID</td>
<td>PO, SC, IV</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>3</td>
<td>Q72h</td>
<td>PO</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Maropitant</td>
<td>1</td>
<td>SID ≤ 5 days</td>
<td>SC</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Vitamin K₁</td>
<td>0.5-1.0</td>
<td>Q12h X 3</td>
<td>SC</td>
<td>Lipidosis</td>
</tr>
<tr>
<td>L-carnitine</td>
<td>250-500</td>
<td>SID</td>
<td>PO/tube</td>
<td>Lipidosis</td>
</tr>
<tr>
<td>Arginine</td>
<td>250</td>
<td>SID</td>
<td>PO/tube</td>
<td>Lipidosis</td>
</tr>
<tr>
<td>Taurine</td>
<td>250-500</td>
<td>SID</td>
<td>PO/tube</td>
<td>Lipidosis</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>15</td>
<td>Q12-24h</td>
<td>PO/tube</td>
<td>Cholestasis, lipidosis</td>
</tr>
<tr>
<td>S-adenosyl-L-methionine</td>
<td>20-40</td>
<td>SID</td>
<td>PO/tube</td>
<td>Glutathione donor, lipidosis</td>
</tr>
<tr>
<td>Milk thistle (silymarin)</td>
<td>5-15</td>
<td>SID</td>
<td>PO/tube</td>
<td>Hepatoprotective antioxidant</td>
</tr>
</tbody>
</table>

**PROGNOSIS**
Outcome depends on identification of concurrent/underlying problem and the ability to correct or attenuate it. Refractory hypokalemia is a negative prognostic indicator, thus hypokalemia must be addressed early on and aggressively. Should serum potassium levels not respond to standard therapy, serum magnesium should be evaluated. Correction of hypomagnesaemia may make serum potassium levels more responsive to KCl therapy.

**SUMMARY**
Effective treatment of hepatic lipidosis requires commitment to the client as well as client education in discussing the likelihood of an underlying primary disease, the importance of supportive care, without which the condition has a poor prognosis, and encouragement because HL rarely reoccurs. Treatment may require weeks to months of assisted alimentation and metabolic support as well as concurrent management of underling medical conditions. A recovery rate exceeding 85% can be achieved if the primary disease can be identified and ameliorated and the patient survives the initial 72-hours of critical supportive care.

**REFERENCES**


Appendix
cisionally a dissecting abscess of the cervical tissues; these complications are rare and heal shortly after the tube is removed and the local reaction treated appropriately.

Many practitioners prefer to place esophagostomy tubes rather than gastrostomy tubes in all cats that have a functional upper GI tract except those that have esophageal motility disorders, such as megAESOPHagus. The esophagostomy tubes are easier to place, maintain, and remove than gastrostomy tubes. Many caregivers appear to accept esophagostomy tubes over gastrostomy tubes.

**Esophagostomy Tube Placement (Figure 19-4)**

1. The cat is placed under anesthesia and the left lateral cervical skin is clipped and prepared for surgery. The esophagostomy tube (e.g., red rubber feeding tube or JorVet J-390 14 Fr, 9 inch tube) is placed in the mid-cervical region between the lateral spinous processes dorsally and the jugular vein and carotid artery ventrally.

2. A curved hemostat is placed down the mouth and into the esophagus, halfway between the angle of the jaw and the thoracic inlet. The curved portion of the instrument should point laterally.

3. The hemostat is then further directed laterally so that it "tents" the esophagus and overlying skin by pushing the tip against the left lateral esophageal wall. A small incision (0.25-0.5 cm) is made over the tip of the hemostat.

4. A small incision (0.25-0.5 cm) is made over the tip of the hemostat. The jaw is then opened and the tip of the red rubber feeding tube is grasped with the instrument and pulled partially through the skin and out the mouth. The tube is then pushed abradely down the esophagus with the hemostat to the level of the ninth rib. The objective is to allow the tip of the tube to go into the stomach to prevent any vomiting or reflux esophagitis. The esophagostomy tube is then sutured into place and a tight wrap is placed over the tube.
NUTRITIONAL SUPPORT

The key is to make a tiny incision through the esophagus just big enough to see the tip of the instrument. The instrument is pushed through the surgically created hole in the tissue. The jaws of the carminou or hemostat are opened and the tip of the red rubber feeding tube is grasped with the instrument and pulled partially through the skin and out the mouth. The tube is then pushed aborally down the esophagus with the hemostat to the level of the ninth rib. The objective is to not allow the tip of the tube to go into the stomach to prevent any vomiting or reflux esophagitis.

4. The esophagostomy tube is then sutured into place and a light wrap is placed over the tube. Note that a blenderized commercial diet can be fed as soon as the patient can tolerate enteral feeding (Figure 19-5), usually within 24 hours. The amount of liquid provided is generally 25% to 30% of daily need; it is divided, administered every 4 to 8 hours, and then increased daily as fast as the cat can tolerate full feeding. Metoclopramide is often added to enhance normal GI motility.

Gastropony tubes are frequently used for cats that need nutritional support for more than 7 days (Figure 19-6) [14]. These tubes can be placed surgically or with endoscopic guidance. A 5 ml, 18 to 24 Fr balloon-tipped urethral catheter (e.g., Foley catheter) can be placed surgically, as can a mushroom-tipped Pezzer proportionate head urologic catheter. Complications associated with gastropony tubes may include local or diffuse peritonitis, bleeding, cramping, vomiting, and diarrhea.

Gastropony Tube Placement

1. General anesthesia is required for the placement of a gastropony tube. Prior to placement of the tube, the left pericostal area just below the paravertebral epaxial musculature is clipped and prepared for surgery. A 2 to 3 cm incision is made through the skin and subcutaneous tissue just caudal to the last rib to allow blunt dissection through the musculature into the abdominal cavity.

2. The stomach is inflated through a tube that is placed down the esophagus to allow the surgeon to easily locate the stomach through the opening in the abdominal wall. Stay sutures are placed to allow a temporary fixation of the stomach against the abdominal wall; these stay sutures are used later to help close the muscular wall.

3. Two concentric purse-string sutures of 2-0 nonabsorbable nylon suture are then placed deep in the stomach wall; the first purse-string is deep to the second purse-string to allow an overlapping closure.

4. The feeding tube is placed into the lumen of the stomach through a stab incision in the middle of the purse-string sutures. The tip of the catheter generally is clipped off to allow easy introduction of food through the tube and into the stomach.

5. Once the tube is in place, the balloon is inflated with water if the balloon-tipped catheter is used; the Pezzer-tipped catheter has an expanded head that flattens and then returns to its normal shape when a stylet is extended and then removed in the catheter lumen during placement through the stab incision into the stomach.
Diabetes mellitus is one of the two most common endocrine disorders in cats. It is a heterogeneous group of disorders in which insulin production is reduced or in which tissue cells are resistant to the effects of insulin, resulting in impaired glucose homeostasis. From a clinical perspective, regardless of the cause, diabetes mellitus (DM) can be challenging to diagnose and treat in the cat because of their stress-induced hyperglycemia.

The prevalence of this condition has increased over time from 8 out of 10,000 (in 1970) to 124 of 10,000 (in 1999) cats seen at veterinary teaching hospitals (Prahl). The frequency of occurrence also appears to vary with geographic location (0.21% in Swedish cats [Sallander]; 0.43% in the United Kingdom [McCann]; 0.74% of Australian cats [Lederer 2009]), with British and Australian Burmese being significantly over-represented at 3.7 and 3 fold, respectively. Fasting glucose concentrations are higher and glucose tolerance is lower in Burmese cats in Australia, New Zealand and the UK compared to matched non-Burmese cats [Lederer 2005]. It appears to be inherited as an autosomal, not fully penetrant trait in these Burmese.

Pathophysiology Review
Insulin is secreted after a meal, to facilitate utilization and storage of glucose, fat and amino acids in three primary tissues: liver, muscle and fat. A mild insulin deficiency results in decreased transfer of ingested nutrients into tissues causing mild to moderate hyperglycemia. Severe insulin deficiency not only hampers tissue uptake of ingested fuels, but also results in marked compensatory glucose overproduction along with excessive mobilization of the body's protein and fat stores. Combined with glucagon excess (relative or absolute), this results in an increased delivery of fatty acids to the liver, their oxidation to ketone bodies (beta hydroxybutyrate, acetoacetate, and acetone), and a clinical state of ketoacidosis. Because there is no insulin available to deliver the glucose into the cells, cells starve and polyphagia with concurrent weight loss occurs. Unabsorbed glucose (hyperglycemia) spills into the urine drawing water with it. This causes polyuria and compensatory polydypsia.

Classification And Differentiation Between Type 1 And Type 2 Diabetes
In human diabetes, Type 1 refers to a condition of insulin dependency seen in people who are generally lean, young and prone to ketogenesis. It is caused by immune-mediated beta cell depletion, causing an absolute insulin deficiency. Type 2 DM usually occurs in the older human, often obese but less prone to the development of ketoacidosis. The underlying problem is one of insulin receptor and post receptor defects, interfering with insulin uptake by tissues. This insulin resistance and associated hyperglycemia, causes the beta cells to produce more insulin, thus this state is one of a relative insulin deficiency. Type 2 may be controlled, at least initially, with weight loss, diet and oral hypoglycemic agents.

Generally, diabetes is a disorder of the older, often overweight cat, similar to the Type 2 human patient. Risk factors include body weight > 7 kg, older age (> 10 years), male gender, neutered. Henso showed that increased body condition score (BCS) in non-diabetic cats is associated with increased circulating concentrations of IAPP and insulin. Obese cats appear to have a defect in
insulin secretion along with lower tissue sensitivity to insulin. Unlike human Type 2, however, by the time the diagnosis of diabetes is made, most cats are insulin dependent although not prone to ketogenesis. In addition to these differences, cats may also develop diabetes secondary to endocrinopathies (acromegaly or hyperadrenocorticism), or drug therapy (glucocorticoids and progestins). Inflammation is another recognized predisposing factor for susceptible individuals to develop diabetes. Franchini has shown at a molecular level that the inflammation induced by bacterial or viral infection can, via molecules recognized by toll-gate receptors, damage endocrine pancreatic tissue. It remains unclear whether pancreatitis is a significant co-morbidity (Forcada) or whether it may be a) a source of inflammation no different than other sites or b) pancreatitis develops as a result of beta cell apoptosis.

Additionally, in cats pancreatic islet amyloid deposits are believed to interfere with insulin secretion, and that oral hypoglycemics (such as the secretagogue sulfonylureas) may actually increase islet amyloid polypeptide (IAPP) deposition. IAPP is co-secreted with insulin. Islet amyloidosis occurs in 90% of humans with Type 2 DM. (O’Brien)

Thus, feline diabetes shares several similarities with the disease in humans. Impaired beta-cell function, decreased beta-cell mass, insulin resistance that is often related to obesity, and pancreatic amyloid deposition, are among these common features. (Zini March 2010) Unlike humans, DM does not predispose cats to hypertension.

**Diagnosis**

In the stressed patient, epinephrine release causes hyperglycemia and glucosuria. Therefore, even in cats with history and clinical findings of polyuria/polydypsia, polyphagia, weight loss, hyperglycemia and glucosuria, it is essential to differentiate between this stress response and diabetes. This can be done through verifying that the hyperglycemia and glucosuria are persistent over time. However, because stress recurs a better option is to request that a fructosamine level be run on the previously collected sample. Fructosamine measures the protein bound glucose levels over the preceding 10-20 days. It can be affected by protein metabolism as well, hence hyperthyroidism, with more rapid muscle turnover, may result in artificially lower fructosamine values.

Urine ketone measurement is routinely performed in cats with diabetes mellitus to identify impending or established ketoacidosis. The urinary ketone dipstick test has a low sensitivity as it quantifies the less abundant ketone acetacetate. Beta-hydroxybutyrate (beta-OHB) is the predominant serum ketone. Determination of plasma beta-OHB concentration was shown to be a useful method to distinguish between diabetic and non-diabetic sick cats. (Zeugswetter)

**Therapy And Management Of The Diabetic Cat**

Good glycemic control soon after diagnosis is associated with increased probability of remission. Some believe that it should be the goal of insulin therapy. (Roomp, Marshall) In a study published in 2010, clinical remission of diabetes was evaluated. Ninety cats with newly diagnosed diabetes were followed until death or remission. Remission was defined as normoglycemia without insulin for ≥ 4 weeks. Likelihood of remission was found to be greater in older cats and in cats with higher body weight. Remission was less likely in cats with increased serum cholesterol and was of shorter duration when serum glucose was higher, i.e.,
less well regulated. (Zini, Nov 2010).

More recently, Gostelow et al performed a literature review on feline remission. They found that the quality of the studies was lacking and biased especially regarding lack of randomization and blinding, small sample size and, most tellingly, a lack of consensus in criteria for defining remission as well as even the diagnosis of diabetes.

**Insulin Choice:** There are many types of insulin available: they are derived from several sources and have several durations of action. In the United States, the FDA has eliminated any animal sourced insulin from the market. Insulins are currently produced from human recombinant technology. However, beef-pork and beef sourced insulins may be better suited to cats because of closer structural similarity to feline insulin.

**Speed Of Onset And Duration:** The speed, onset of action and duration differs between insulins.

1. **Regular (fast)** - rapid onset of action (0.5h), max. effect (1-5h), end effect (8h)
2. **NPH (intermediate)** - onset of action (1.5h), max. effect (4-12h), end effect (24h)
3. **Lente** - onset of action (2.5h), max. effect (7-15h), end effect (24h)
4. **Semilente** - onset of action (1.5h), max. effect (5-10h), end effect (16h)
5. **Combination: 70% NPH: 30% regular** - onset of action (0.5h), max. effect (4-8h), end effect (24h)
6. **Ultralente (long acting)** - onset of action (4h), max. effect (10-30h), end effect (36h)
7. **Synthetic insulin analogues:** glargine and detemir (ultra-long acting) once a day in humans

These values are for comparison only and reflect human metabolism. **Insulin responses vary with the individual. Every cat is different and will respond differently to the insulin they take in the management of diabetes.** It is ALWAYS advisable to start with an insulin that is licenced for veterinary use.

**Vetsulin™,** is a 40 U/ml porcine lente zinc insulin specifically registered for veterinary use. It has been available for over 15 years as Caninsulin around the world and is known as **Vetsulin™** in the United States. Its peak activity is ~3h and duration of 6-10h. It is very effective for the treatment of feline diabetes.

Protamine zinc insulin (PZI) is a long-acting, beef-pork insulin that was considered by many to be the insulin of choice for cats because of its molecular similarity to feline insulin. Since November 2009, an FDA approved recombinant human protamine zinc insulin preparation, **ProZinc™,** has come on the veterinary market. Like Vetsulin/Caninsulin, it is a 40 unit/ml (U40) insulin.

**Humulin N** and **Novolin N** are recombinant human NPH insulins (100 U/ml) that have an intermediate duration of action. They do not work well in most cats.

**Glargine** (Lantus™) is a long-acting human recombinant DNA insulin analogue that has been modified by replacing one amino acid (asparagine) with another (glycine) as well as adding 2 arginine amino acids to the c-terminal end of the molecule. This changes the pH solubility making it microprecipitate at the site of subcutaneous injection that are slowly absorbed. This
should result in fewer troughs and a slower, smoother glycemic effect, however this does not appear to occur in all cats. Because the formation of microcrystals and slow absorption are dependent on the acidity of the product, glargine cannot be mixed or diluted.

Interestingly, in cats with diabetic ketoacidosis, glargine may be used in place of regular (Toronto) insulin if given IM or IV. By these routes, it has a similar action profile to that of regular insulin. In fact, in some resistant diabetic cats, one might consider using it by both the IM and SC routes BID with 70% of the dose given SC and 30% of the dose given IM.

**Detemir** (Levemir™) is another long acting human rDNA analogue. It is modified from insulin by adding an acylated fatty acid chain. This allows reversible binding to plasma proteins, resulting in a slow release into plasma. In cats, its action and duration are similar to those of glargine. The dose required may be less than that of glargine (~30% less in the Gilor study). Remission rates and time to remission are similar.

**Newer Insulin Analogues:** Rapid-acting insulin analogues lispro, aspart, and glulisine act by blocking the formation of insulin dimers and hexamers. This allows larger amounts of the active monomeric insulin to be immediately available for postprandial use when given at mealtime. Studies in dogs and cats have yet to been reported.

Insulin degludec (Tresiba™) is a new-generation, ultra-long-acting analogue not yet available in North America or Europe. It forms large soluble multi-hexamers at the injection site. Studies in dogs and cats have yet to been reported but, due to its extremely long action in humans (given once daily or three times a week), it might provide reliable once-a-day or once-every-other-day therapy in cats.

A concept not used in veterinary medicine but that may help with some difficult diabetics is that of combining insulins to have one that provides **basal control and** another covering **mealtime** glycemic needs (basal-bolus therapy). In humans, this approach is taken using premixed combinations of a short-acting and a longer-acting or ultra-long-acting insulin analogues. While not yet studied in cats (or dogs), this effect might be achieved through giving SC glargine concurrently with an IM dose BID or by using SC Vetsulin or ProZinc concurrently with SC glargine or detemir BID. The insulins must not be mixed in one syringe.

**Concentration:** It is critical to know the concentration of the insulin you are using and to match the syringes to that strength. For correct dosing, insulin should be administered using syringes specifically calibrated for the strength of insulin used. For example, most insulin is 100 Units/ml (U100) and micro-fine or ultra-fine U100 syringes should be used with these. With U-100 insulin, when only small amounts of insulin are needed, using a 3/10cc or 5/10cc U-100 allows even the tiniest dose to be measured more accurately.

The advantage of using a 40 unit/ml insulin is that it is more making it easier to more accurately dose small amounts of insulin. The specific U-40 syringes should be prescribed with this product. As the use of U100 syringes for a more dilute U40 insulin risks miscommunication and tragic consequences.
While there are guidelines in choosing the starting dose of insulin for a patient, the maximum dose for that patient is the dose that he/she needs to resolve the clinical signs of excessive urination and drinking, lethargy and weakness. The majority of cats require twice daily injections, regardless of the type of insulin selected.

Client Counselling
Once the cat has been determined to be diabetic, client counselling is very important. Initially, most clients are intimidated at the thought of administering insulin injections. Booking a discharge or demonstration appointment with the nurse-technologist works well, as nurses are often more patient than veterinarians are at explaining and guiding the learning client.

At this appointment, review the pertinent facts about insulin storage (refrigerator), handling (gently), re suspension (gentle figure 8's), drawing up into the syringe, administration (upon exhalation of client, walk through the door of the tent, OR pull the tent over the needle, think canvas, practise on a cat using saline), single use only of insulin syringes for sterility and sharpness sake.

Show the client how to keep a diary, recording date, time of insulin administration, dose administered, activity level, BM, amount urinated (# and size of clumps of clumping litter), amount eaten, and amount drunk (by difference, measure amount left in bowl the next morning).

Counsel on diet to be fed, as determined by the veterinarian. Lower carbohydrate, higher protein diets may be more effective for glycemic control, however this remains controversial. There is no scientific consensus on carbohydrates: to date there is no clear evidence that carbohydrates either cause or are contraindicated in the treatment of feline diabetes (Farrow, Coradini, Sallander, Slingerland, Owens, Hoenig). The native diet for a cat (bird or mouse) is high protein, moderate fat, low carbohydrate, it is reasonable to feed this macronutrient profile for any cat. Cats should have free access to food all the time, rather than feeding twice daily.

Some cats refuse to eat the diets we recommend. For those patients and for clients unwilling/unable to offer those diets, here is a website which lists the protein and carbohydrate proportions of grocery store brands: http://www.sugarcats.net/sites/impeerson/. Other helpful websites for clients to use for information, support and encouragement (including teaching techniques) follow: www.petdiabetes.com, www.felinediabetes.com, www.sugarcats.com and www.cat-dog-diabetes.com/cats-diabetes-mellitus.asp

Cats with comorbidities that require a different diet should be fed the diet appropriate for their concurrent disease. Insulin dose can be regulated with consistent feeding of any diet. Similarly, should a diabetic cat need prednisolone for a concurrent problem (e.g., asthma or inflammatory bowel disease [IBD]), treat the underlying problem as needed and regulate the insulin to that corticosteroid dose. If the antiinflammatory action can be provided through a non glucocorticoid agent, (e.g., chlorambucil for IBD, an NSAID for arthritis), then that can be attempted.

Monitoring urine parameters at home is justified for:
- Cats with transient diabetes - to identify when/if glucosuria recurs
- Cats on oral hypoglycemics to determine if glucosuria resolves
- Cats previously or currently ketoacidotic - to monitor for ketones

**Follow-Up Care And Monitoring**

At the discharge time, book an appointment for a blood glucose curve and re-evaluation for 14 days later. Let the client know that you will call daily for the first 3 - 4 days, to be supportive and available for questions, to find out how the kitty is doing, and to ascertain that they are observing the parameters you need diarized for evaluation. Let them know that it is unlikely that the initial dose will be the perfect one, and that, as they approach the "right" dose for this cat, there will initially be a marked reduction in urine output and drinking, however, after 3-4 days, these amounts will increase again as the cat's glucose homeostasis re-equilibrates.

The timeline for care that the author uses is:

- Diagnose diabetes mellitus by confirming with fuctosamine; start insulin, diet and diary;
- 10-14 days later: in-clinic BG curve, adjust dose, teach ear prick BGs, add BID BG monitoring to diary for practice;
- Another 10-14 days later: in-clinic BG curve, fructosamine, adjust dose;
- Subsequent BG curves are performed at home, follow-up by email, phone or fax to adjust dose;
- Recheck cat q4-6 months (exam, fructosamine, U/A) as long as he/she is stable.

At the **blood glucose (BG) curve** appointment, hospitalize the cat with food and water, after weighing him/her and ascertaining what time the insulin was administered and what dose the client gave. Measure BG immediately, to get a starting level. Using a 25G needle works well, as a mere drop or two of blood are needed for the portable glucometers. Plot the values on a graph for easier interpretation. Submit a serum fructosamine as well to determine how the average glycemic control has been over the past 10-20 days.

Continue measuring the BG every 1 (-1.5) hours over a 12 hour period. Ear sampling and a calm, reassuring manner will help to minimize the stress (and its associated BG elevations) somewhat. Nevertheless, the readings generally will be higher than what is occurring at home, therefore it is imperative to read the client's diary and take the clinical signs into consideration when adjusting the insulin dose. Once the blood glucose goes up for two consecutive measurements, the curve can be stopped. (Note this does NOT apply in the case of a cat in diabetic ketoacidosis.)

Use of the marginal ear vein is an accurate and easy technique for the measurement of BG. It is a useful technique in the clinic and, if the concept is introduced to clients with confidence and compassion, many are willing to perform curves at home. In general, these curves are more accurate as the cat’s stress level is lower. Additionally, it is valuable for clients to be able to measure a spot glucose if their cat “doesn’t look right” before deciding to give insulin or not.

The goals of performing a BG curve are to determine

1) Whether the insulin is being absorbed
2) The glucose nadir (level and time to reach it)
3) The duration of insulin effect
4) The degree (delta) of insulin effect, and
5) To assess the fluctuations of glucose levels in this individual patient!

When using glargine, the protocol for regulation and curving is somewhat different. The following recommendations come from Dr. Jacque Rand:

- Measure glucoses every two hours for a minimum of 12 hours daily for the first three days in order to determine whether hypoglycemia is occurring as well as to assess how long the insulin is lasting in the individual. After this initial three day period, dose adjustments are based on the pre-insulin BG (vs. nadir as with other types of insulin).
- If at a 7 day hospital recheck, the pre-insulin BG concentration is > 290 mg/dl (16 mmol/L), increase the dose by 1.0 U/cat. A 12h curve should be done on the following day to make sure that hypoglycemia is not occurring at this increased dose.
- Do not change the dose if the pre-insulin BG concentration is 220-290 mg/dl (12-16 mmol/L).
- The dose should be decreased by 0.5-1.0 U/cat if the pre-insulin BG concentration is < 180 mg/dL (10 mmol/L). If biochemical hypoglycemia is present, the dose should be decreased by 1.0 U/cat. If clinical signs of hypoglycemia are present, the glargine dose should be decreased by 50%.

If a BG drops below normal range (< 80mg/dl or < 4.4 mmol/l), the staff person should notify the veterinarian after offering the cat some palatable food, as he/she may wish to administer dextrose intravenously to avoid a **hypoglycemic crisis**. Signs of hypoglycemia include weakness, lethargy, trembling, head tilt, ataxia, coma and death. If a hypoglycemic cat is offered food and doesn't eat right away, or if signs are severe, then corn syrup should be rubbed on the oral buccal mucosa while preparing to administer an intravenous dose of 50% dextrose.
The "**Somogyi effect**" is rebound hypoglycemia-induced hyperglycemia. If the cat's BG drops too low, the body reacts by releasing catecholamines (epinephrine), glucagon, glucocorticoids and growth hormone. This causes a rapid release of glucose into the serum causing this rebound to occur. It is important to *not* be tempted to increase the insulin dose in these individuals, as this would accentuate the problem and eventually cause a hypoglycemic crisis. "Spot checks" of BG levels should be avoided as they can be misleading and can mask a rebound effect, and be misinterpreted as needing more insulin.

Over the next month or two, by performing blood glucose curves, measuring serum fructosamine and reassessing the cat clinically and historically (diary) every 2 weeks, the insulin dose suitable for this patient **will** be determined. Thereafter, it is advisable to see the stable diabetic cat every 4 - 6 months for a fructosamine. Consider, also, on these rechecks, to collect a sterile urine sample for urinalysis, as diabetic cats are more prone to bacterial urinary tract infections than non-diabetic individuals. If a diabetic patient becomes ill, then a glucose curve should be run as well as any other tests appropriate to their condition.

**Update on glucometers:**
In a study comparing AlphaTRAK, Ascensia ELITE and reference hexokinase methods for determining serum glucose, the AlphaTRAK meter results did not differ from the reference method, however results from the Ascensia ELITE were significantly lower. The superior performance of the AlphaTRAK meter supports its use to monitor blood glucose levels in cats. (Zini, 2009)

**Useful resources**

**Complete references are available from author on request**
Blood glucose curves can be very helpful to determine the dose and type of insulin for a given cat. They are not difficult to interpret when simple rules are followed. It is very important to get a reading every hour. Cats should have food available at all times.

1. Start by looking at the shape of whole curve. Identify the nadir (lowest BG value), time to nadir, starting and highest BG value, duration (Figure 1).

**Figure 1. Elements of a blood glucose curve**

Check if the blood glucose (BG) level decreases for a reasonable period of time. This indicates that cells see and respond to the insulin?
- If the curve merely wobbles around the starting level (e.g., curve D in Figure 2), then either:
  - The cells do not see/respond to this insulin;
  - The client is not administering the insulin correctly. This could be technique (intra-fur, intradermal resulting in poor absorption) or lack of comprehension (giving air, wrong dose);
  - The insulin is damaged (dropped, client wiped vial with alcohol, bacteria introduced into vial);
  - Counter-regulatory phase of Somogyi response to overdose.

2. Time between BG at time zero (just before insulin is given) to time at which BG level is the same = duration of action. This value tells you how long the insulin lasts in this individual.
- If duration is 9-12h, then BID administration is appropriate;
If duration is 6-8h, then TID administration is appropriate.

3. Time to reach nadir indicates how rapidly insulin is being absorbed and taking effect. If peak insulin effect is between 2-4h after administration, be suspicious of Somogyi overswing (too much insulin). This will be followed by a rapid increase in BG with the curve exceeding the starting BG.

4. BG level at nadir indicates maximum effect of insulin. IMPORTANT In order to determine nadir, one must have hourly BG readings. In fact, to really identify the nadir, we would need even more frequent readings, however with less than hourly measurements, we could easily miss a Somogyi, both at nadir as well as the overswing.

5. Glucose differential/delta is the difference between starting BG and nadir BG. If this difference is small (<7 mmol/L; 126 mg/dL), it is easy to decrease the starting BG without dropping the BG too low at nadir. This is a safe insulin to use for this patient. If the difference is large, it becomes difficult to increase the dose without risking hypoglycemia at peak effect.

6. Goal range for BG (not to be confused with differential) of 5.5-12 mmol/L; 100-215 mg/dL throughout the day provides good glycemic control and normalizes fructosamine levels.

Spot checking should only be done to determine whether a lethargic, wobbly cat is hypoglycemic (and needs glucose) or hyperglycemic (and needs insulin) before rushing the cat to the clinic. Using spot checks (i.e., anything less than hourly measurements) does not provide useful information and can result in making inappropriate recommendations.

Fructosamine reflects glycemic control, or time that BG is above ideal range over approximately the preceding 10-14 days. It is elevated if too little insulin is given but will also be elevated during Somogyi overswing, i.e., when too much insulin is being given. Glucosuria will occur under both situations as well.

**Figure 2. Examples of blood glucose curves**
A Ideal curve => continue dose and type of insulin
B Short duration => give insulin more often or change type of insulin
C Somogyi overswing: rapid drop in glucose with counter-regulatory overcorrection => decrease insulin dose or change type of insulin
D Poor response due to client misunderstanding, poor technique, damaged insulin, attempt to correct from Somogyi response, extremely low dose => Client education, recheck curve. If no change, change insulin.
Useful resources
RESPECTFUL CAT HANDLING vs. CAT WRANGLING:
Part 1 - FROM THE CAT’S POINT OF VIEW
Margie Scherk, DVM, DABVP (feline practice)
Vancouver, BC, Canada

INTRODUCTION
In many clinics, some veterinarians and other team members do not enjoy working with cats because they believe that cats are unpredictable and feel anxious about getting hurt. By understanding why cats feel that they need to defend themselves, by learning to identify the warning cues, managing the interactions in a positive manner, and making relatively minor changes to what the cat is exposed to, this fear can be reduced.

The basis for working cooperatively with cats is being empathic to their nature and behaviors and trying to imagine what their experience is like. Cats are a species with a social structure different from ours. We need to look at cats differently, slow down and adjust our interactions. Minor modifications to the physical facility help reduce the strangeness and threats that cats experience in the veterinary clinic.

The goal of these two presentations is to look at how to change the experience for cats thereby removing some of the obstacles to routine feline veterinary care. This benefits cats and their human companions with the resulting side effect of clinic growth.

WHY CATS RESPOND THE WAY THEY DO
In the wild, the number of feral cats living together depends on the availability of resources. These are food, water, privacy and safety, toileting areas, and availability of sexual partners. Mice and small birds are single portions; they are not large enough to be shared. After weaning, cats are responsible for feeding themselves. The resource density determines the number of cats living in a given area. In order to reduce conflict and the potential for physical harm associated with fighting, cats have developed an impressive repertoire of signals to maintain distance and protect resources within their territory. This results in little competition and a social structure that does not require sharing or taking turns. Stress is minimal unless resources become scarce. Aggressive communication signals developed in order to keep distance between individuals and to prevent contact with outsiders. Cats need to avoid physical injury in order to be able to hunt and protect themselves. When resources are plentiful, a colony will develop consisting of related female cats with their young, who they jointly defend and nurse. Males are relegated to the periphery and vie for breeding privileges; only one mature tom usually lives with the group.

Many of the behaviours cats show in a clinic situation stem from the fact that while they are predators of mice and small birds, they are prey relative to almost all other larger animals, including larger birds. When they feel threatened, they rely on “fight or flight” and will try to escape situations that they view as dangerous. When they can’t flee, they fight (self-defense) or freeze. From the perspective of a cat, humans are, (and what we do is), dangerous. As a result, we see frightened and defensive cats every day. Cats try to avoid physical confrontation through by using intimidating sounds and postures. This small creature feels more threatened than we do; it is important to refrain from becoming frightened ourselves.
Reading and understanding the cues and signals that cats use is important to detecting incipient fear. This allows us to respond respectfully as well as redirect the progression of an emotion and reshape experiences. We can learn to avoid using signals that are hostile (e.g., scruffing, making shushing/hissing sounds, looking into their faces) when we know how cats communicate.

**FELINE SIGNALING: READING THEIR CUES**

**Tactile Sense**

Touch is very important to cats. They rub against each other (allorubbing), against us, and against inanimate objects. Whether a full-body rub or rubbing a flank, tail, cheek or other body part, rubbing is believed to be an affiliative behavior seen between members of the same social group, feline or human. Rubbing is not only tactile, but is also a means of depositing the colony (family) scent. Cats often rub against us; unfortunately, we often misinterpret it as a request to be fed.

Allogrooming (mutual grooming) may precede a playful attack, follow a stressful interaction, and appear to be conciliatory or may simply be grooming. Kneading and treading occurs in adults either as a kitten-regressive behavior or as a component of sexual interaction.

The neck bite/scruffing is used by cats in three contexts: for transportation of young kittens, for restraint during copulation, and for dominance in a fight. Our use of scruffing fits most closely with the last and does not promote shaping safe, respectful cooperation. (See AAFP and ISFM Feline Friendly Handling Guidelines.)

**Olfactory Cues**

The role of smell and scent in feline communication is something we human beings are ill-equipped to appreciate. It has been estimated that the size of the olfactory epithelium in cats can be up to 20 cm², whereas humans have only 2 to 4 cm² of olfactory epithelium. While olfactory signals may be left by several methods, the one that is most problematic for people is urine spraying. This is a potent and important method of communication that we fail to appreciate. Other forms of olfactory messaging are cheek marking an object or individual, scratching to leave scent from glands below the footpads, and midden, (i.e., leaving a deposit of feces uncovered in a strategic place). All of these have several advantages over visual cues. The message persists over time and in the absence of the sender, allowing for remote communication without the potential for conflict that direct interaction risks. This is especially useful at night and in areas with poor visibility. These signals help cats spread out over space as well as time-share territory. The disadvantage of this form of communication is that the sender cannot change the message once it has been deposited; it cannot be altered or removed and no adjustments can be made in response to the recipient’s reaction. So, urine marking in the home is an attempt to signal to the other cats when “I was ‘here’” and to establish a routine so that the cats can keep a distance by time-sharing the same space without needing to come into conflict. Every time we remove the urine, we interfere with this communication!

Because of our less well-developed olfactory sense, we fail to “read” the signals a patient may be giving us and are unable to fathom the overwhelming olfactory messages from previous patients and substances used in the hospital that the clinic experience presents to cats.

**Visual Cues: Body Language (Posture, Face, Tail)**
Body language and facial expression are extremely effective at maintaining or increasing distance between individuals potentially competing for resources. This requires having an unobstructed view, adequate ambient light, and, unlike olfactory cues, that the two individuals are in the same space at the same time. Body posture cues the big picture of emotional state but facial expression (eyes, ears, whiskers, mouth, visibility of teeth) provides the finer details and changes more rapidly. In a clinic setting, for us to appreciate the mental/emotional state of an individual, to avoid provoking them and getting hurt, it is extremely important to watch and interpret facial changes.

As a species that generally leads a solitary existence, survival depends on speed, stealth, self-reliance, and outsmarting others. As a consequence, cats may “bluff”. When they act aggressively, they are generally hiding fear; “stoicism” hides vulnerability; subtle changes in behavior mask pain or significant illness. Body postures communicate confidence and physical prowess that may not be present. Keeping a threat at a distance may eliminate the need for a physical confrontation. The arched back “Halloween cat” typifies this façade of confidence. Making oneself smaller, on the other hand, to minimize threat and evade attention is portrayed by a crouch and withdrawal. In these postures, the weight remains on all four paws so that flight or chase remains possible. A cat feeling less fearful does not need to be on his or her feet. However, an extremely fearful threatened cat will roll exposing his or her abdomen with all four feet ready for self-defense. This cat may be screaming while showing all of its weapons (nails and teeth).

Cats have extremely mobile ears. When the ears are forward, a cat is listening and is generally relaxed or alert but not emotionally aroused. Turned laterally, flat “airplane ears” indicate that the cat is more fearful or feels threatened. When ears are back and tight to the head, the cat is feeling very threatened and frightened. This cat will have a partially or fully open mouth and be hissing, spitting, yowling, or screaming. Cats will protect themselves if we fail to reduce the level of perceived threat. Ears turned back but erect indicates the most reactive and aggressive state. In this case, the mouth will be closed and the cat will be emitting a low growl with or without swallowing. This is the cat to be apprehensive of.

**Vocalization**
This form of communication requires the direct presence of the recipient. It has the benefit of being easy to adapt from moment to moment. As with other signals, cats have a well-developed repertoire of sounds to convey a need or wish to increase the distance between individuals. The sounds made for encouraging socialization are a trill/chirrup, purr, puffing, prusten, chatter, miaow, and sexual calling. The cat that is open-mouth screaming is highly aroused but is probably less aggressive than the cat that is close-mouthed growl/wah-wah/mowling.

Cats use a combination of these different signals in any situation. We have to learn to look for all of them and interpret them together.
Figure 1. Interpreting a cat’s body posture.

Figure 2. Interpreting a cat’s ear position and facial expression.
INTRODUCTION
Making the clinic environment more “feline friendly” requires imagining how a cat perceives it. The exercise becomes one of identifying potential threats and removing or reducing their significance.

Reducing Threats In The Hospital Setting
It is important to reduce exposure to true predators (dogs, people, other cats) and to other perceived threats. Visual barriers in the seating/waiting area help to prevent cats from seeing dogs. Covering the carriers with a towel will also help so that cats don’t see each other. Using chairs or ledges, keep kennels off the floor. If possible, have a separate cat-only waiting area. Reserve at least one examination room only for cats in order to reduce the smells of predators and to be able to furnish it with necessary items for examining cats as well as to strive to achieve cat comfort.

Looking over our clinic/hospital environment, what can we do to reduce the stress and threat level of the physical and social environment? What things or events assault the five senses of a cat? How can we make positive changes to these? Table 1 shows a chart that can be completed by the clinic team. For example: Scary smells include alcohol, disinfectants, odours of other carried animals; this can be remediated by wiping the area to which alcohol had sparingly been applied with a damp cloth and using venipuncture sites far from the nose (medial saphenous) when possible. Disinfectant should be allowed to evaporate before a cat is placed/replaced in a kennel. Carry and examine all patients in their own, fresh towel rather than have their smells embed themselves in your clothing.

Table 1. Chart For Evaluating Perceived Threats To Cats In Hospital Setting

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<th>Sense</th>
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<th>Reduce threat by</th>
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<td>Hearing</td>
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Handling (Examination, Hospitalization, Diagnostics, And Treatments)
The goal is to handle our patients respectfully and provide an appeasing environment to build positive, long-term relationships. This is achieved by reducing threat and, thus, the cat’s need to
react defensively. Avoid doing things in a way that use threatening feline body language or tone. The aggressive cat is upright, stiff-legged, and large; sit down to examine cats.

Never stare a frightened cat in the face: examine cats from behind and, other than for ophthalmic evaluation, avoid direct frontal facial viewing. Using a sideways glance with hooded eyelids indicates a desire to cooperate. A slow blink is a reassuring signal to a cat similar to a human smile.

The aggressive cat growls and uses low tones; use light, upper register tones, perhaps chirruping as cats do when they are relaxed with conspecifics. Shushing a cat to try to calm her as we might a child is the equivalent to hissing at her. Short repetitive sounds should be avoided, since these may resemble spitting rhythms. Purrs, chuffing, trills, and chirrups are welcoming sounds. When cats feel secure and safe, even just able to hide their faces in an elbow or a towel, they allow most procedures. Try to keep all four of their paws on the floor and avoid changing their body position as much as possible. A comprehensive examination, blood and urine collection, body temperature and blood pressure evaluation can all be done without changing the cat’s position. Examine her in the base of her own carrier if the lid can be removed. Don’t hang a cat’s forelimbs over the edge of a table for jugular venipuncture. For the frightened individual, additional lack of support under the paws is not reassuring.

Reaching into a kennel to pick up a patient blocks the light; to the cat you appear as a looming, frightening stranger (smells, sounds, visual input). Instead, approach the opening of a kennel from the side so that some light still enters. Do not block every chance for escape; if the possibility to have some control over her environment and situation exists, she will be much more cooperative. Because cats rely on flight and fight for survival and are not reliant on others, when it comes to restraint, the mantra holds true: Less is more! Cats inherently resist intimate handling and restraint. By restraining them, we take away their sense of control and cause them to react. It is very easy to condition negative emotional responses. Scruffing is strongly discouraged as it is an act of dominance that cats may resent. Similarly, stretching is an inappropriate, disrespectful and unnecessary way to apply restraint. Every future experience builds on the previous negative (or positive) experience. Cat bags, masks, and gloves all carry the scents of similarly terrified patients plus other sundry smells (anal gland secretion, pus, blood, halitosis, etc.) A towel is all that is needed to wrap a cat in, in order to protect the handler. Remember, a cat would rather flee than attack.

Train all staff in respectful cat interactions and handling. An excellent and comprehensive resource is the American Association of Feline Practitioners (AAFP) and International Society of Feline Medicine (ISFM)’s Feline Friendly Handling Guidelines, downloadable at: www.isfm.net/wellcat/UK/FFHG.pdf. It is well worth reviewing and refining cat examination techniques as a clinic team for a consistent approach, the goal being to make them less threatening. Because value is “perceived worth” and because every visit is a valuable opportunity to educate the client, talk to the client and the cat throughout the entire procedure. Source and provide feline friendly medications, being sure to follow up one or more times with the client to find out how the patient is doing and if the client needs a refresher course on how to administer the medications. Be sure to send home an exam report with home care instructions for the client to refer to. Schedule recheck appointments or the next wellness visit before the client leaves the
practice. The AAFP has created the Cat Friendly Practice program through which any interested clinic can raise its cat care IQ. (catfriendlypractice.catvets.com)

Meeting Environmental Needs Improves Health
Recently, it has been recognized that emotional well-being is highly dependent on meeting the environmental needs of cats. These include those relating to the indoor and outdoor physical environment, as well as a cat’s social interactions, human and otherwise. In the AAFP and ISFM Feline Environmental Needs Guidelines, five pillars are described that form the basis of a healthy feline environment (Ellis, 2013). These pillars are:

1. A safe space
2. Multiple and separated resource stations (food, water, toileting areas, scratching areas, play areas, perches, resting and sleeping areas)
3. Opportunity for play and expression of predatory behaviors
4. Positive, consistent and predictable interactions with humans
5. An environment that respects the importance of a cat’s sense of smell

When these are not met, cats become stressed to varying degrees. Some may express illness (such as inflammatory bowel disease, lower urinary tract inflammation), while others will manifest their distress through inappropriate elimination.

Other Considerations
As cats age, they tolerate less time in the clinic. Siamese cats are especially prone to becoming depressed. Three days may be as long as a cat can stand the anxieties and indignities of hospitalization, even with daily visits from the owner. Consider capping intravenous catheters and send patients home, having them return for outpatient care. Even for in-hospital care, capping catheters off overnight (administering the overnight dose via the subcutaneous route) allows greater ease of movement, avoids alarms, which keeps patients awake. In either case, administer the overnight fluid volume subcutaneously.

Because cats “see” the world in overlapping clouds of smells, we should strive to provide familiar smells and reduce foreign, medicinal smells. Client-worn shirts or toys from home are helpful in cages. Feline facial pheromone may help to reduce stress. Because cats’ sense of hearing is tuned more finely than ours, a quiet and reassuring environment is desirable. Cats should not be exposed to the sounds of predators, namely barking dog, but strange machines (faxes, printers, phones, dishwashers, centrifuges, etc.) should also be addressed. Reducing noises should be addressed when using certain induction agents as some enhance hearing (e.g., ketamine).

Avoid changing a cat’s diet during hospitalization as is likely to result in inappetence and possibly the development of an aversion. If a change in diet is required for therapeutic reasons, try to make that change gradually in the safety of the home territory.

Taking a thorough history is especially important given cats’ tendency to hide illness. Listening carefully to clients and their concerns is extremely important. Often clients detect changes that represent real problems. This is probably more common than the client who is blissfully unaware of significant health problems. By asking open-ended questions, we elicit a more detailed history than using only specific questions. For example, asking, “Have you noticed any changes in the
contents of the litter box?” will probably evoke a yes or no answer. Whereas: “What does his stool look like?” followed by: “Would you describe it as hard pellets, moist logs, cowpie, or colored water? What colour is it? When did you first notice this?” will probably provide more useful answers. “Is there anything else?” is a very effective question.

Schedule a recheck appointment to evaluate the effect of any medical or nutritional therapy. Reassessing important variables (e.g., body weight, body condition score, previously abnormal laboratory results) and updating the patient history allows us to provide better care for our feline patients. Care of the client is essential to providing complete patient care. It is only through listening to, educating, and working with the client that we are able to offer the very best veterinary care.

Examples of practical applications
1. If a cat is uncooperative, a comprehensive physical examination can usually be done using only a towel as a protective barrier. Facing the cat away from you is less threatening for her. Confining the cat between your legs as you sit on the floor provides adequate persistent firm restraint that is reassuring rather than frightening.
2. Swaddling a cat’s forelimbs and torso may help with blood and urine collection, placing the cat in lateral recumbency for cystocentesis and using the medial saphenous vein. This vein is also a superb choice for catheter placement and administration of intravenous medications. If the cat is allowed to have her front end in a sternal position while the back end is in lateral recumbency, she may struggle less.
3. Allow the client to be with the kitty as much as, and whenever, possible.
4. Recognize that a persistently elevated systolic value above 160 or 170 mm Hg probably represents true hypertension rather than the stress response. If in doubt, repeat the value later during the visit.
5. Feliway™ (Ceva Animal Health), a synthetic analog of a feline facial pheromone, may have a calming effect on cats. Spray (or wipe) it into kennels and carriers and even on your clothing before handling an anxious cat. Let the substance evaporate for a few minutes before placing the cat into the sprayed space. Feliway diffusers plugged into treatment and hospitalization areas as well as reception and consultation rooms can help patients relax.
6. Elevated blood glucose and glucosuria may be a result of persistent stress. A diagnosis of diabetes, therefore, should be confirmed by finding an elevated serum fructosamine.

RECOMMENDED READING
1. Buffington CAT. Cat Mastery – e book from iTunes
7. Hide Perch Go and Cat Sense: www.spca.bc.ca/welfare/professional-resources/catsense/