



### What Makes Cats Tick? Feline Internal Medicine Module 1 : Mellow Yellow : Winning With Hepatic Lipidosis

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**Abstract:** Using a clinical case, the diagnosis and intensive therapy for hepatic lipidosis discussed.

Ginger comes in with her "mom". Complaint: decreased appetite for 1 week, hasn't eaten anything for 2 days now; low energy; retching yesterday and today, only bringing up clear froth, maybe a little yellow at the end; urinating but not defecating for past 4 days; is a strictly indoor cat, "current" on vaccines; very quiet, "not her spunky self!" Ginger is a 4-year-old DSH tabby. She was drinking water on her own. Thinks she has lost weight. Previous exam 9 lbs Today's exam: BW 7 lbs., lethargic, quiet and a little dazed, spiky coat, thin, moderate skin tent with tacky oral mucous membranes, pink, crt 1.5 seconds moderate dental calculus with mild gingivitis, halitosis, yellow hue on soft palate, slightly sunken eyes, mild bilateral crusty ocular discharge, HR=180, RR=48, t=38C (101.5F), BP (Doppler) RH size 3 cuff 148 Thoracic auscultation: no abnormalities; abdominal palpation: doughy abdomen, moderate sized bladder, liver margins easily palpated and rounded, no stool in colon, no evidence of pain; dandruff over tail base.

What is our problem list? Inappetence/ anorexia of 9 days, weight loss (2 lbs, 22%), icterus, dehydration, dental disease, palpable liver margins (hepatomegaly?), depression, vomiting.

What are our differentials? Hepatic Lipidosis-primary vs. secondary to other disorders, cholangiohepatitis, cholangitis, cholecystitis, toxic hepatopathy, extra-hepatic bile duct obstruction, intussusception, gastroenteritis: viral, bacterial, endoparasitic, GI foreign body, pancreatitis, pancreatic cyst or abscess, cholelithiasis, neoplasia (e.g. gastric pushing liver back), hepatic, intestinal lymphoma, adenocarcinoma, pancreatic neoplasia, acute pyelonephritis, diabetic ketoacidosis, or diabetes mellitus FeLV/FIV/FIP. Also, anything that may cause hemolysis including hemobartonella, onions, drug related oxidative injury or IMHA, zinc toxicosis, autoimmune hemolytic anemia.

How are we going to help this kitty? What diagnostics and therapeutics do you recommend? Let's collect blood for a CBC, differential, chemistry panel with electrolytes, T4 and lipase, FeLV and FIV, I'd run a PCV/TS, glucose in house, collect urine by agitated cystocentesis for u/a and hook her up to IV fluids at a rate calculated for deficit and maintenance. I'd add 35 mEq KCl to a liter of fluids to start with. We'd start syringe feeding her modestly with a/d to begin with and institute anti-emetic therapy if she appeared nauseous.

#### Pathogenesis

The development of lipid vacuoles within hepatocytes does not directly have a noxious effect on the cell. It is believed that the lipid accumulation reflects an underlying metabolic disorder. For example, any systemically ill person is expected to have some fat vacuoles in their hepatocytes. The problem is when the lipidosis is morphologically severe. In a normal feline liver, the fat content is less than 5% of the total hepatic weight. The liver of a cat with lipidosis may double or triple in weight from the accumulated/retained fat.

Fat in the liver is of five types: 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

Fat metabolism: Regulation of fat metabolism in the adipocyte may be a major factor promoting lipidosis. Many cats developing hepatic lipidosis (HL) are obese. Unrestricted release of fatty acids from excessive adipose fat promotes lipidosis because up to one third of mobilized fat may be residing in the liver at one time. Therefore, in these cats, lipidosis may reflect the liver's inability to match fat dispersal with delivery from systemic sources.

The balance of TG lipolysis and accumulation is modulated by blood glucose concentration as well as hormonal, neural and pharmacological mechanisms. The activity of hormone sensitive lipase and lipoprotein lipase directly regulate adipocyte fat metabolism. Hormone sensitive lipase (HSL) promotes lipolysis. Norepinephrine, epinephrine, growth hormone, glucagons, corticosteroids and thyroxin increase HSL activity. Insulin inhibits HSL. Cats release catecholamines very readily, thus, stress may exacerbate HSL activity and fatty acid metabolism. The absence of insulin would act similarly.

Adipocyte lipoprotein lipase (LPL) activity promotes fat uptake in the well-fed individual. In starvation, LPL activity declines, while HSL increases. Thus, lipolysis exceeds fat uptake. A previously obese individual undergoing starvation is at increased risk for lipolysis.

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 the formation of very low-density lipoproteins (VLDL). Requirements for VLDL particle dispersal include 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.

Studies looking at the ultrastructural components of hepatocytes in hepatic lipidosis have shown a reduced number of peroxisomes, which are organelles needed for oxidation of long chain fatty acids prior to transport into the mitochondria. This would result in impaired beta-oxidation and lipoprotein dispersal.

Given the complexity of lipid metabolism, it is, however, unlikely that one pathogenesis explains HL in all affected individuals. Possible scenarios include:

- An increased presentation of fat to the liver as a result of obesity,
- Catabolism,
- Chronic overnutrition,
- Decreased in novo hepatic fatty acid synthesis,
- Decreased beta oxidation of fatty acids, and
- Impaired dispersal of VLDL from the liver.

### Signalment

Obese female cats are at greatest risk of developing hepatic lipidosis. Cats of any age may be affected; most commonly cats are between 4-15 years of age. Domestic shorthair cats are breed predisposed; this finding could be a reflection of this breed's greater incidence in the population.

### History

Clients bring their cat in because of weight loss or anorexia, vomiting, lethargy and weakness. While fat may become depleted on the limbs and dorsal trunk, abdominal and thoracic fat stores remain spared.

### Physical examination findings

- Dehydration
- Pallor of mucous membranes
- Icterus
- Unkempt appearance
- Hepatomegaly

### Rules Of Lipidosis

#### **RULE #1** with yellow cats: **FEED FIRST, DIAGNOSE LATER!**

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 contra-indicated unless encephalopathy is present. Dietary management of IHL cats should closely resemble their natural diet - that is, a higher protein, and lower carbohydrate diet. They also improve clinically when arginine, carnitine and B vitamins are added to the treatment regimen. In cases of hepatic encephalopathy protein levels should be supplied at 30-35% protein, as in a recovery or maintenance diets or proteins should be composed of minimal quantities of aromatic amino acids in order to reduce the production of false neurotransmitters.

Ginger's blood work came back: normal CBC except a slightly lowered MCV and with moderate poikilocytosis. Biochemistry: increased alt with greater increase in sap, ggt high normal, slight increase in bilirubin, slight hyperglycemia and mild hypoalbuminemia. FeLV/FIV negative. U/A USG 1.045, bile staining, bilirubinuria, ketones, a few bile crystals. Let's look at these: Because she is icteric but her PCV was normal, we know that she is not having a hemolytic crisis. Thus, the icterus is hepatic or post-hepatic. Her cholesterol wasn't massively elevated (thus not extrahepatic bile duct obstruction), nor was it low (thus not portosystemic shunt, terminal cirrhosis, or end stage liver failure). Urine bilirubin is ALWAYS significant in the cat, so it confirms and supports the bilirubinemia. Her T4 was normal, so the liver enzyme alterations aren't due to hepatocellular injury or cholestasis. There may be mechanical bile stasis from hepatocellular swelling causing narrowing of the bile canaliculi, but this is different from increased alk phos production of thickened bile. The hypoalbuminemia may be more significant than it looks, especially in a dehydrated cat. The loss doesn't appear to be renal, so maybe it is gut loss. A clinically significance of the hypoalbuminemia is to remember to reduce doses of protein bound drugs (e.g. metronidazole, many sedatives including valium, antibiotics, cardiac drugs, metaclopramide) in these patients. Avoid unnecessary drugs in cats with hepatic disorders. The hyperglycemia is likely stress induced. Now, what about the urine ketones without any glucosuria?

The underlying problem in a lipidotic cat is their dysfunctional lipoprotein and lipid metabolism, particularly in the transport and accumulation of VLDL (very low density lipoprotein)...i.e. fatty acids. In a starving cat, adipocyte lipolysis is promoted due to reduced glucose availability, decreased insulin concentrations, increased concentrations of growth hormone and glucocorticoids. The fatty acids are taken into the liver where, in a healthy liver, they are oxidized to ketone bodies or re-esterified to triglycerides (TG). In the lipidotic liver, increased TG storage occurs and ketone metabolism may be altered, resulting in ketonuria. One way to check if these ketones are from lipolysis, rather than diabetes, is to run a serum beta-hydroxybutyrate level. Of course, confirmation of diabetes can be made via a) history and clinical findings, along with b) serum fructosamine or glycosylated hemoglobin levels to differentiate stress-induced hyperglycemia/glucosuria.

**RULE #2** of yellow cats: **FLUIDS!** Treat and prevent dehydration with a non-lactate and non-glucose containing fluid. Lactate metabolism requires hepatic input. Glucose requires hepatic metabolism. Hydration is critical; dehydration decreases hepatic circulation, which impairs detoxification. It also increases the urea in the gut, which results in azotemia, increased ammonia production and absorption. Constipation (often a result of dehydration) allows prolonged contact with endotoxic materials in the gut. A dehydrated cat with severe liver disease will feel very ill as he/she is, in essence, undergoing a continuous ammonia challenge test. Pectin and lactulose may be beneficial as pectin traps H<sup>+</sup> and lactulose incorporates N into bacteria.

Classical biochemical pattern is an increased SAP, a less increased alt with bilirubinemia/-uria and normal or only slight increase in ggt. Also, on ultrasound, a hyperechoic appearance is supportive of the diagnosis of lipidosis.

**RULE #3** of yellow cats: **LOOK FOR THE UNDERLYING CAUSE OF THE LIPIDOSIS** Ultrasound to assess 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. It is important to try to determine which cats have concurrent pancreatitis, because in one study, 38% of cats with HL had concurrent histopathologic acute pancreatitis. The recovery rate of cats with acute pancreatitis was 20%

rather than >50% of cats with HL alone. Note: most people report a much higher recovery rate of 50-80% of cats with lipidosis and I want YOU to be getting upwards of 80% recovery! When you have a patient with hepatic lipidosis, primary or secondary...the point is to feed first, diagnose later. We see a hyperechoic liver, in this case. We have the option of doing a fine needle aspirate (FNA), a Tru-cut (TC) or wedge biopsy of the liver.

Fine needle cytology gets better samples if you use a passive technique (i.e. redirect the needle several times but do not have it attached to a syringe. This way you won't disrupt the cells. Attach the syringe to the needle once you come out of the tissue and then blow the cells out of the needle onto slides; make the impressions or smears gently to avoid creating "road kill". If you use standard active FNA technique, you will cause cell disruption and will collect only lipidotic hepatocytes, rather than having a chance of getting stroma and other cell types. Tru-cut gives you a chance to get some architecture/histopathology, which tells you more about the disease process (es) than cytology does. Histopathology of wedge biopsies gives you the best samples (and information) of course, as well as allowing you to collect other organ samples as well. To recap... Get an abdominal ultrasound and histopathology of the liver rather than cytology. If other organs are affected, consider surgery to get multiple organ biopsies (plus g-tube placement) if the patient is stable enough and once coagulation factors and electrolyte abnormalities are corrected. Ultrasound will be useful...that is why we recommend u/s first.

**RULE #4** of yellow cats: **FEEDING VIA LARGE BORE TUBE INCREASES CHANCE OF SURVIVAL.** Esophageal or gastrostomy tubes are easily placed and maintained.

**VOMITING!** For vomiting patients, metaclopramide is more effective and less neuropathic when given by constant rate infusion (1-2 mg/kg cri IV over 24 hours). For volume induced vomiting, "trickle feed" by putting the diet into an empty fluid bag and running it by constant slow drip through the g-tube.

Selected anti-emetics for use in the cat		
Generic Name	Product™	Dose (feline)
Chlorpromazin	Thorazine, Largactil	0.5 mg/kg q8h IM
Prochlorpromazine	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	8.0 mg/kg q8h PO
Prochlorpromazine + Isopropamide	Darbazine	0.5-0.8-mg/kg q12h IM, SQ
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 q24h

**RULE#5** of the yellow cat: FEED 60 Kcal/kg healthy body weight/day of a good quality, calorie dense diet is essential. Protein restriction should only be considered in the cat with hepatic encephalopathy (uncommon). FEED A DIET WITH ADEQUATE PROTEIN rather than a protein restricted diet. Protein should be > 20% of calories. Don't use carbohydrates instead of fat, as these cats are already prone to insulin resistance. Arginine is an essential amino acid in the cat (easy to remember: Carnitine-Arginine-Taurine = CAT). Arginine is needed for normal detoxification of nitrogen. Cage resting cats with HL may reduce muscle release of ammonia, thus may be beneficial. 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.

**RULE#6: SUPPLEMENTATION WITH L-CARNITINE** 250-500mg PO q24h increases the chance of recovery. L-carnitine is an essential cofactor of fatty acid (fa) metabolism. Sources are meat and dairy. It can be synthesized endogenously from lysine and methionine. L-carnitine transforms free long chain fa into acyl- carnitines and transports these into mitochondria. L-carnitine prevents accumulation of free fa in the hepatocyte cytoplasm as well as acetyl groups in the mitochondria. Accumulation of these substances is toxic causing injury to the organelles and resulting in an energy deficit. Cats in HL are in a "relative-local hepatocellular carnitine deficiency" regardless of their muscle carnitine levels.

**TAURINE SUPPLEMENTATION** with 250-500 mg/day is valuable as this is an essential amino acid in the cat. Taurine may be hepatoprotective and is required for bile conjugation. It plays a role in membrane stability and function. Cats with HL are taurine wasting in their urine. Anorexia causes a decrease in serum taurine levels.

**RULE#7 VITAMIN K SUPPLEMENTATION.** 50% of cats with HL have prolonged PIVKA (Proteins Induced in Vitamin K Absence or Antagonism) times or other prolonged coagulation tests and require Vit K1 therapy. It takes cats < 7 days to become Vit K deficient. Cats who have been on antibiotics may have fewer organisms in their bowels to make Vit K. Vitamin K is absorbed in the proximal small bowel and recycled by the liver (Vit K epoxidase cycle). Thus, in small bowel disease (such as IBD induced fat malabsorption), as well as in liver diseases (especially in hepatic lipidosis), low Vitamin K levels may predispose to occult coagulopathies. Factors II, VII, IX and X, as well as protein C and protein S (antithrombotic proteins) are Vit K dependent. Supplementation is most effective using Vit K1. If the patient is jaundiced or nauseous, then the Vit K1 must be given SC rather than orally because intestinal absorption is poor (0.5-1.0 mg/kg q24h X 3-4 days or until coagulation normalizes.) If too much Vit K1 is given, an oxidative toxicity may develop and supplementation of Vit E as an antioxidant may be required. (A Vit K responsive coagulopathy has been reported in Devon Rex cats in Australia. They may be subclinical and asymptomatic; the problem is due to inefficient enzyme activity.)

**RULE#8 SUPPLEMENT WATER SOLUBLE VITAMINS** Thiamine supplementation is indicated in cats with ventroflexion of the neck if serum potassium levels are normal. Vit B12 is required for lipoprotein

production.

**RULE#9 CORRECT SERUM POTASSIUM** Aggressive attention to and correction of serum hypokalemia is essential; hypokalemia is a negative predictor for survival. 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. One more thing about hypokalemia: hypokalemia alters the threshold of response of neuroreceptors.

**RULE#10** Because bile canaliculi are narrowed, consider using ursidol. **URSODEOXYCHOLIC ACID** is a 'synthetic' bile acid, which has a number of hepatoprotective effects. It also provides IgA to proximal duodenum. It requires taurine for conjugation. Uses include any hepatic condition in which cell swelling interferes with bile flow through canaliculi. Cholecystitis with or without sludging of bile is an indication for using ursidol (Actigal, Ursofalk, 15 mg/kg PO q12-24h). The blood brain barrier permeability is affected by bile acids; this may be another reason why patients on ursidol feel better. Patients with liver disease may develop gastric vasculopathies due to abnormal gut circulation altering mucosal barrier, permitting gut wall edema and GI ulceration. Remember that GI hemorrhage (or a blood transfusion before surgery) is like a blood meal for these patients, and it affects their nitrogen balance and ammonia handling.

S-adenosyl-L-methionine (**SAMe**, Denosyl SD4) 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 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.

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