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OPTIMIZING CARE FOR HEPATIC LIPIDOSIS

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Hepatic lipidosis (HL) is a syndrome that develops secondary to anorexia caused by a primary health problem in >90% of cats, or as a consequence of starvation.

PREVIOUS DIAGNOSIS

Based on signalment, physical and clinical features, and abdominal ultrasound and aspiration cytology (after vitamin K1 [24 hrs]). Liver biopsy is not necessary for diagnosis but may be required to confirm an underlying primary liver disease (later). Cytosolic vacuolation in >80% of hepatocytes. DON'T be in a hurry to acquire a liver biopsy as these cats have high risk for anesthetic / surgical complications during initial hospitalization.

BLEEDING TENDENCIES

Vitamin K1 responsive coagulopathy is common. Treatment 0.5-1.5 mg/kg SQ or IM, 3 doses at 12-hr intervals. Never give IV. Avoid inserting jugular catheters, cystentoscopy, or placing esophagostomy- or gastrostomy-tubes before vitamin K repletion.

BODY CONDITION ASSESSMENT

Estimated lean body mass guides fluid and drug dosing in overconditioned cats.

FLUID THERAPY

Avoid dextrose supplementation (promotes hepatic fat accumulation and hypokalemia (urine wasting). Lactate intolerance may exist: avoid lactated ringers. Acetate metabolism also may be compromised. Initially use: 0.9% NaCl, supplemented with electrolytes and B-vitamins.

WATER SOLUBLE VITAMINS

Liver stores and activates many water soluble vitamins. Inappetent cats show susceptibility for both thiamine and cobalamin depletion. A doubled daily maintenance dose of fortified water soluble vitamins (thiamine: 50 mg/ml) is recommended: 2 ml/L fluids. Fluids containing B-vitamins should be protected from direct light.

THIAMINE (VITAMIN B1)

Thiamine deficiency is suspected in some cats (central vestibular signs, dilated pupils, head/neck ventroflexion, abnormal postural reactions, hyperthermia, hypotension) based on treatment response. Supplementation is essential prior to feeding, thiamine requirements increase with carbohydrate metabolism. Avoid injectable thiamine (rare, lethal anaphylactic / vasovagal response has been observed), use oral tablets 50 to 100 mg PO BID and Fortified B-vitamin solution in fluids, slowly administered.

VITAMIN B12 (COBALAMIN)

Encountered in cats chronically malnourished with small intestinal disease; B12 deficiency imposes metabolic circumstances favoring HL. Supplementation: 0.5 to 1.0 mg/cat given first day of hospitalization, AFTER collection of baseline sample. Baseline and sequential testing permits tailoring of chronic supplementation.

FAT SOLUBLE VITAMINS

may require supplementation secondary to enteric malabsorption (impaired enterohepatic bile acid circulation) or inadequate reserves. Vitamin K1, give as soon as HL considered (first 12-hrs); proven to ameliorate common coagulation abnormality (detected with PIVKA testing). Parenteral dosing necessary; 0.5 and 1.5 mg/kg, repeated three times at 12- hour intervals. Low vitamin E (γ-tocopherol) suspected but unproven to complicate HL based on circumstantial evidence: low liver glutathione (GSH), Vit. E depletion in similar hepatic disorders (humans, experimental models), vitamin K insufficiency (fat soluble vitamin), and bile acid profile consistent with impaired enterohepatic circulation (causing fat malassimilation). Treatment provides antioxidant protection for lipid and water soluble cell constituents, may protect against oxidative challenges imposed by cholestasis. Use water soluble form of γ-tocopherol PO, dose: 10 IU/Kg/day.

THIOL DONOR SUPPLEMENTATION

Similarities between feline HL and kwasiorkor, proven low liver GSH, susceptibility to heinz body hemolysis, cholestatic injury, and suspected low vitamin E each argue for thiol supplementation. Thiol donors can preserve/replete GSH. Crisis Rx N-acetylcysteine (NAC) first few days: loading dose or 140 mg/kg of NAC (20% solution diluted 1:4 with saline or 5% dextrose), then 70 mg/kg given BID to TID. NAC given IV through 0.25 µm nonpyrogenic filter over 20-minutes, avoid constant-rate-infusion (CRI) as this may impair urea cycle ammonia detoxification. Initiate oral enteric coated SAMe tablets (Denosyl-SD4™, Nutramax, Inc.) after 2-3 days; dose: 180 mg dose per cat (35-60 mg/kg), PO SID to BID. Enteric coating improves bioavailability, crushing tablets and administering with food reduces bioavailability (BID dosing may help?).

ELECTROLYTE ABNORMALITIES

Electrolyte abnormalities are an important cause of patient morbidity and mortality. Hypokalemia, hypophosphatemia, and/or hypomagnesemia are initially identified in 30%, 17%, 28%, respectively. Severe hypokalemia and hypophosphatemia increase risk for hemolysis (hypophosphatemia), muscle weakness, "silent" gut atony thwarting feeding attempts (vomiting: associated with gastric, intestinal, or esophageal stasis) head ventroflexion, inability to concentrate urine (promotes dehydration), and neurobehavioral changes confused with hepatic encephalopathy. Head ventroflexion also may reflect thiamine deficiency. Hypokalemia imparts neuromuscular signs and cardiac arrhythmias when < 2.5 mEq/L (membrane hyperpolarization). Hypokalemia is significantly associated with failure to survive.

ANTICIPATE RE-FEEDING PHENOMENON

Potentially lethal condition involving severe electrolyte and fluid shifts associated with sudden metabolic adaptations in malnourished patients upon initial re-feeding (enteral, or parenteral). HL cats have heightened risk. Shifted metabolism promotes insulin release and cell uptake of glucose, phosphate, potassium, magnesium and water, and enhances protein synthesis. Nutritional support magnifies cell requirements for phosphate, potassium, glucose and water and increases demand for ATP, 2,3 diphosphoglycerate.
(2,3 DPG), and creatine kinase (CK). Hypokalemia: most common electrolyte abnormality potentiated by re-feeding. Severe hypophosphatemia common within 48-hours: clinical signs develop when phosphate < 1.5 mg/dl. Symptomatic hypomagnesemia is uncommon but effects can be profound and confused with hypokalemia or hypophosphatemia. Thiamine deficiency also may manifest in unsupplemented patients owing to its utilization in enzymatic reactions involving glucose.

**POTASSIUM SUPPLEMENTATION**

Initial KCl supplementation using conventional sliding scale; rate restricted to < 0.5 mEq/kg/hr. Judicious titration is tailored to effect based on twice daily potassium assessments during the first week. Essential to account for all potassium sources during supplementation to avoid iatrogenic hyperkalemia (KCl and K phosphate supplements).

**PHOSPHATE SUPPLEMENTATION**

A starting CRI of K phosphate: 0.01 to 0.03 mmol/kg/hr is given at initial feeding, but may require upward titration. Phosphate status must be monitored twice daily to avoid oversupplementation; otherwise, K phosphate is slowly tapered over 36 hours after sustained phosphate concentrations proven.

**MAGNESIUM SUPPLEMENTATION (RARELY NEEDED)**

Acute treatment: IV Mg using magnesium sulfate (8.13 mEq/g) and magnesium chloride (9.25 mEq/g) salts, (available as 50% solutions) but given as 20% solutions (or lower) in 5% Dextrose and water. Initial dose: 0.75 to 1.0 mEq/kg/day administered by CRI for first day, with lower dose of 0.3 to 0.5 mEq/kg/day given for an additional 2-5 days (slow restitution of Mg stores in true deficiency). Treat overdose with calcium gluconate (IV), 50 mg/kg slow bolus followed by 10 mg/kg/hour constant rate infusion (CRI).

**NUTRITIONAL SUPPORT-INITIAL FEEDING**

Oral or nasogastric (NG). Use NG if cat objects to oral feeding (salivates, vomits, struggles) to avoid feline food aversion. NG tube (5-8 french) inappropriate for long term feeding (nasopharyngeal discomfort, retroflexion during emesis, requires Elizabethan collar) although some cats have been recovered this way.

**ESOPHAGOSTOMY (E-TUBE) / GASTROSTOMY (G-TUBE) FEEDING**

Placed after improved hydration and electrolyte status, vitamin K\(_1\) therapy; E-Tubes are associated with fewest critical complications.

**E-Tube**

10-12 French; avoid highly pliable silicone tubes that are easily retroflexed. A thoracic radiograph is mandatory after E-tube placement; verify appropriate tube position cranial to gastroesophageal junction (insertion into stomach increases risk for reflux esophagitis).

**G-Tube**

Mushroom tipped (not foley catheters) > 20 French permit greater food variety, easier feeding, amenable to trickle feeding approach. Best placed percutaneously using endoscopy; biopsies of stomach and duodenum collected if appropriate. Surgically placed G-tubes impose greater risk and suffer more complications. Premature G-tube removal (within 2 –3 weeks) may lead to septic peritonitis.

**FEEDING TUBE CARE**

Maintain tube hygiene by flushing with tepid water after use; use minimal volume necessary. Avoid giving congealing medications via tube. Aspirate G-Tube before feeding to evaluate gastric emptying: > 10 ml indicates gastric hypokinesia (check electrolytes, tube related problems). Site of tube insertion should be inspected daily (first 10 days); any discharge cytologically inspected (is it food or infection?). Triple antibiotic ointment and a supportive aseptic wrap are recommended; some cats require an Elizabethan collar to prohibit tube mutilation/removal. Bandages concealing G-Tubes should have tube outline traced on surface to prevent accidental cutting during bandage change. Tube occlusions are resolved with solutions that can digest food: Coca Cola, papaya juice, or pancreatic enzymes. Retain solution for 20-40 minutes then hydropause with tepid water.

**PERSISTENT VOMITING**

Consider: electrolyte derangements (enteric hypomotility), nausea (hepatic disease or drug therapy), G-tube dysfunction/displacement (pyloric obstruction), or underlying primary disease (IBD, pancreatitis). Tube investigation may require contrast radiography or ultrasonography. Changing “meal” feeding to “trickle feeding” eliminates emesis in some. Trickle feeding: use infusion pump and a liquefied diet, feeding daily requirements 12 to 24 hour interval. Best done using G-tube but also accomplished with NG-or E-tubes. Re-new food q 4-6 hours to avoid bacterial contamination. With G-tube monitoring of residual volume may monitor for gastric hypokinesis: q 8- to 12-hours, if volume > hourly delivery rate, discontinue feeding for several hours, evaluate electrolytes and other potential causes, reduce hourly feeding rate by 20%. Continued trend of high residual gastric volume warrants evaluation of tube position with imaging.

**ANTIEMETICS**

After ruling out correctable causes of emesis. Metoclopramide (Reglan\(^\text{®}\)) as CRI (0.01-0.02 mg/kg/hr IV per 24 hours) in cats trickle fed, or as a bolus dose in cats meal fed (0.2 - 0.4 mg/kg SQ 20-30-minutes before feeding, 4 doses per day). Alternative antiemetic: Ondansetron (Zofran\(^\text{®}\)), a 5 HT\(_3\) receptor antagonist mediating nausea/vomiting via chemoreceptive trigger zone. Dose: 0.1 to 0.2 mg/kg q 6 to 12 hours. Butorphanol: may provide an antiemetic effect when combined with other antiemetics; use low dose: 0.1 mg/kg SC q 12 hours. Exercise: may stimulate enteric motility; 15-30 minutes free walking in a non-stressful environment (no barking dogs) during owner visitation and before feeding in meal fed cats.

**APPETITE STIMULANTS**

Appetite stimulants (e.g. diazepam, clonazepam, cyproheptadine) are unreliable for ensuring adequate energy intakes. Diazepam requires hepatic biotransformation and imposes risk (albeit low) for idiopathic fulminant hepatic failure; injectable diazepam delivers an oxidant challenge (propylene glycol). Idiopathic hepatotoxicity observed with clonazepam and cyproheptadine given as appetite stimulants in cats. Propofol, suggested as an antianorexic in inappetent cats is strongly contraindicated: pro-oxidant, sedative, and potential mitochondrial toxicity.
FEEDING
Provide adequate energy and protein to avoid catabolism; 60-80 kcal of metabolizable energy/kg ideal body weight. A balanced feline diet should be used, protein restriction is strongly contraindicated. Liquid enteral human formulas lack adequate taurine and arginine/citrulline for cats and require supplementation.

FEEDING REGIMEN
Initial feeding of 15 ml lukewarm water at 2-hr intervals, 2-to 3-times discloses likelihood of emesis /gastric atony. Food then progressively introduced over 2-4 days to achieve 250 to 400 kcal/day for average sized cat. Initial feeding delayed 24-hrs after G-tube placement to allow return of gastric motility and formation of an initial wound seal. Feeding via E-or NG-tube may be initiated after full recovery from the procedure. Daily food intake is divided into 4 or more meals; some require trickle or continuous feeding to achieve total energy allotment.

L-CARNITINE (CN) SUPPLEMENTATION
Hepatic CN synthesis may be limited during catabolism, or secondary to hepatic dysfunction or substrate unavailability (lysine, SAMe, Fe2+, Vitamin C, succinate, and pyridoxal phosphate). Ability to strategically provision appropriate CN for hepatic fatty acid (FA) oxidation/dispersal to achieve a net negative hepatic FA flux remains undetermined. Oral CN (medical grade) is bioavailable, proven to increase FA oxidation in obese cats undergoing weight loss, to attenuate hepatic TG accumulation in an experimental HL model, and may facilitate urinary elimination of CN-esterified FA. Dose: 250-500 mg CN /cat per day using a medical grade CN product (ensures bioavailability).

AMINO ACID SUPPLEMENTATION
Taurine
Short-term taurine (essential amino acid) recommended: low plasma taurine concentrations in HL, obligatory use of taurine for bile acid conjugation, and high flux of conjugated bile acids into urine. Taurine also influences other physiologic/metabolic processes important in HL (e.g. membrane calcium flux, membrane stabilization, detoxification reactions, and antioxidant protection). Dose: of 250 mg/day for 7-10 days (longer if a human enteral diet fed).

Arginine
Supplementation (essential amino acid) recommended if a human enteral diet or designer diet is fed as these may not contain sufficient arginine for urea cycle function. Dose: 1 gram/ 8 fl oz can (250 mg/100 kcal) diet.

Ursodeoxycholic Acid (UDCA)?
I do not recommend UDCA in HL: 1) all bile acids impose cytotoxicity in high concentrations (bile acids are extremely high in HL), 2) high bile acids impair hepatic TG egress, 3) no evidence that UDCA improves similar disorders (humans, rodents), 4) HL has no necroinflammatory/fibrotic component for which UDCA is prescribed, 5) HL recovery is acute, before UDCA may impart benefit, and 6) cholestasis in HL is associated with canalicular dysfunction /compression.

Drugs to Avoid
A number of drugs are specifically contraindicated in HL, including: stanozolol (a 17-alpha alkylated steroid); tetracyclines; drugs imposing oxidative challenge: propylene glycol carrier in diazepam and etomidate, propylene glycol semimioist food preservative, propofol, onion powder flavoring, cetacaine and benzocaine; high dose buprenorphine; sedatives / drugs requiring glucuronidation (diazepam, oxazepam); and drugs associated with idiopathic hepatic necrosis (benzodiazepines, cyproheptadine). Care must be taken in calculating appropriate vitamin K dose.

Predicting Recovery
Clinical recovery is demonstrated by gradual reduction in serum enzymes and total bilirubin concentrations. Generally, within 10 days bilirubin concentration declines by ≥50% while serum enzyme activity may remain near admission values. Cats recovering require approximately 10 days of hospitalization; those succumbing typically do so within 7 days. Some survivors require protracted hospitalization (up to 21 days).

Do Supplements Make a Difference?
Nutritional support with a premium cat food (e.g. Maximum calorie, a/d) with or without metabolic supplements in cats surviving the initial 96 hours (n=86 supplements, n=36 no supplements) suggests that supplements significantly improve survival.