Helping Charlie: A Study of Feline Weight Loss

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I. Weight Loss in Cats
   a. WL is one of the major clinical signs in a plethora of feline diseases.
      i. Poor appetite, lethargy, weight loss
   b. Tracking weight in your feline patients is highly desirable.
      i. Doing so helps to motivate owners to permit diagnostic workups.
      ii. Electronic medical records permit you to do this easily.
   c. The Big Four Differentials
      i. Hyperthyroidism
      ii. Chronic renal disease
      iii. Diabetes mellitus
      iv. Chronic small bowel disease
         1. Chronic Enteritis, usually due to Inflammatory Bowel Disease
         2. Lymphoma of the small bowel.

II. Our patient: Charlie, 12 yr. old, Mn, DLH
   a. History and Physical Exam
      i. Why is hair length significant?
      ii. Quantifying weight loss
         1. Body Condition Score: Scales 1-5 and 1-9; Ideal 3/5 or 5/9
         2. Muscle Condition Score: 1-4; Ideal 1/4
      iii. Three Reasons We Should Question an Owner’s Answers
         1. Owners often give a cover-up answer to hide not knowing or not being observant.
         2. They don’t want to be criticized for waiting too long to see veterinary help.
         3. This is a long-haired cat that is losing weight.
      iv. PU/PD
         1. What question to ask? ____________________
      v. Polyphagia
         1. Multi-cat households are a problem when the cats are free-fed.
      vi. Abdominal Palpation
         1. Masses: Most in GI tract or lymph nodes
         2. Thickened small bowel loops
         3. Renal size and shape.
   b. Laboratory Tests
      i. HCT = 24%
         1. What is the feline normal compared to the canine normal?
         2. How long do feline RBCs live?
      ii. Platelet Count = 143 (200-500)
         1. Automated feline platelet counts are usually much lower than actual due to platelet clumping.
         2. There are no common thrombocytopenic diseases in cats.
         3. If the platelet is low, assume machine error and look at a blood smear.
      iii. Potassium = 3.0 (3.4-5.6)
         1. K is the main electrolyte in contraction of skeletal muscle. Low levels result in muscle weakness that leads to anorexia.
      iv. Liver enzymes
         1. Alkaline phosphatase = 220 (10-90)
         2. ALT = 556 (10-100)
         3. What do LEs mean?
         4. Can they be normal when significant liver disease is present?
      v. Creatinine = 0.8 (0.3-2.1); BUN = 16 (10-30)
vi. Phosphorus = 3.9 (2.4-8.2)
   1. Why 8.2 as the high end of the normal range?
   2. P can help one understand true renal function.
      a. Muscle loss lowers creatinine values.
      b. BUN is affected by many pre-renal conditions.

vii. SDMA = 11 (0-14)
   1. Not affected by muscle wasting, diabetes, or liver, Cushing’s or heart disease.
   2. Not influenced by hemolysis, icterus, or lipemia.

viii. Total T4 = 12.9 (1.5-4.8)
   1. Specificity nearly 100%
   2. “In older cats with supportive clinical signs, total T4 has a high sensitivity, and serum concentrations will be increased in over 90% of cases.” *
   3. False negatives
      a. Mild HT: The trough value of TT4 due to normal day-to-day fluctuation may be in the normal range in early HT.
      b. Concurrent non-thyroidal illness will lower the TT4, which may cause the value to be normal in early HT.

ix. Total T3
   1. “Measurement of total T3 concentration offers no real advantage over total T4 in the diagnosis of feline HT. Serum total T4 and T3 concentrations are highly correlated in HT cats. However, over 30% to 40% of HT cats have serum total T3 concentrations that remain within the reference interval, rendering it a much less sensitive test for diagnosing HT than total T4 determinations.” *

x. Free T4 = 190 (1-14)
   1. The sensitivity is slightly higher than total T4.
   2. However, specificity is much less.
   3. Up to 30% of sick euthyroid cats will have high fT4 concentrations.
   4. “Given the poor specificity of free T4 for diagnosing feline HT, results should be interpreted with caution, especially in cats with normal T4 values. It is not recommended as a sole diagnostic criterion for confirmation of the disease.” *
   b. Mooney CT, Little, CJI, Macrae AW. Effect of illness not associated with the thyroid gland on serum total and free thyroxine concentrations in cats. JAVMA. June 15, 1996.

xi. Thyroid stimulating hormone (TSH) = 0.01 (0.03-0.15)
   1. There is no feline-specific TSH test.
   2. The canine test is commonly used.
   3. “10% of euthyroid sick cats and 15% of healthy cats have subnormal TSH values similar to those in HT cats.” *

xii. Systemic blood pressure = 185/105
   1. Elevated due to: hyperthyroidism, chronic renal disease, stress (white coat)

c. Summary: Charlie’s Clinical Signs & Lab Findings
   i. Weight loss (8.8#)
   ii. PU/PD
   iii. Polyphagia
   iv. Tachycardia (HR=245 bpm)
   v. Murmur (3/6)
   vi. Anemia (PCV=24%)
   vii. Thrombocytopenia (Platelet Ct=143)
   viii. Hypokalemia (K=3.0)
   ix. Elevated LEs (AP=220; ALT=556)
   x. Normal Creatinine and BUN (0.8, 16)
   xi. Normal Serum Phosphorus (P=3.9)
   xii. Normal SDMA (11)
   xiii. Elevated TT4 (12.9)
   xiv. Elevated fT4 (190)
   xv. Low TSH (0.01)
III. The Diagnosis
   a. TT4 = 12.9
   b. Creatinine = 0.8
   c. What mechanism results in the renal function being affected by hyperthyroidism?
      i. Increased HR -> Increased BP -> Increased blood flow through the kidneys (a filter)
   d. How is that affected by the stage of hyperthyroidism?
      i. Early HT does not increase HR or BP to the degree of advanced HT so renal function is not as affected in early HT.
   e. Is the BP high enough to warrant treatment?
      i. Yes No
   f. If so, what treatment is indicated?
      i. ACE-i? Amlodipine? Make the cat euthyroid?

IV. Thyroid Palpation
   a. The Study: J Fel Med Surg; June 2000
   b. Sizing based on palpation and practice
      i. 1=0.5 cm; 2=0.75 cm; 3=1.0 cm These are typically non-functional.
      ii. 4=1.5 cm; 5=2.0 cm; 6=2.5+ cm These typically result in hyperthyroidism.
   c. Technique (See Web Video in The Feline Patient, 5th edition.)
      i. The cat is standing, and you are behind it. Lift its chin 45° and turn it 45° AWAY FROM the side you are palpating. (right side)
      ii. Put the tip of your index finger in the groove between the muscle and the trachea just below the larynx. (right index finger)
      iii. Slide your finger downward to the thoracic inlet. ONLY go up-to-down in direction.
      iv. You will not feel most lobes until your finger goes past them. There will be a characteristic “pop” or “thyroid slip.”
      v. Change hands and palpate the other side.
      vi. Repeat palpation on both sides.
   d. How can a cat be hyperthyroid, and the palpation be 0 and 0?
      i. Technique failure.
      ii. Intrathoracic migration of a cervical lobe.
      iii. Thyroid tumor in intrathoracic ectopic thyroid tissue.

V. Technetium Scan
   a. A radioactive isotope is injected, and the cat is scanned for its uptake in thyroid tissue.
   b. A very sensitive and specific test for thyroid enlargement (hyperthyroidism?).
   c. Thyroid lobe and ectopic thyroid tissue enlargement is detected.
      i. Ectopic hyperthyroidism occurs in about 2% of HT cats.
   d. Indications
      i. Diagnosing HT when the clinical signs are present and the TT4 & fT4 are normal.
      ii. Detecting extra-lobar thyroid adenomas.
         1. ***This is important if surgery is to be performed.
      iii. A technetium scan cannot differentiate benign vs. malignant tissue.
      iv. Of minimal use if methimazole, y/d, or I131 is used for treatment.
      v. “Use of thyroid scintigraphy to identify the location of all functional thyroid tissue prior to surgery helps avoid persistent hyperthyroidism. Thyroid scintigraphy will differentiate unilateral versus bilateral involvement and can also identify ectopic thyroid disease, large thyroid adenomas or carcinomas that have descended into the chest, and thyroid carcinomas that have metastasized.” (Broome MR, Peterson ME, Treatment of Severe, Unresponsive, or Recurrent Hyperthyroidism. Consultations in Feline Internal Medicine, 2016)

VI. T3 Suppression Test
   a. For cats with palpable thyroid gland, clinical signs of HT, and normal TT4/fT4.
   b. Protocol
      i. Collect and freeze serum.
      ii. Give T3 orally (Cytomel 25 mcg; q8h X 7 doses)
      iii. Collect serum 2-4 hours after the last dose.
iv. Submit pre-pill and post-pill serum samples together.

v. Request T3 and T4 on both samples

c. Interpretation
   i. Normal cat ("suppression"): the post-pill TT4 is <50% of the pre-pill TT4.
   ii. Hyperthyroid cats do not suppress because the thyroid tumor is acting independently of 
       negative feedback on the pituitary gland.
   iii. Purpose of the T3s
        1. To validate the test.
        2. If it does not go up significantly, the owner did not give the tablets or the cat did 
           not swallow them.

iv. Note: Dispense or prescribe 10 tablets so there are spares in case of pilling failure.

VII. Summary of Norsworthy’s Diagnostic Approach to Hyperthyroidism Based on:
   a. Age of the cat: 8+ years old.
   b. Correct clinical signs, especially weight loss.
   c. Thyroid palpation
   d. TT4
   e. T3 suppression test, if TT4 is normal.

![Diagram of Norsworthy's Diagnostic Approach to Hyperthyroidism]

VIII. Treatment Options
   a. Two Categories
      i. Control: Iodine-restricted diet and Methimazole
      ii. Cure: Thyroidectomy and Radioiodine
   b. All treatment options have pros and cons. There is not one treatment option that is the right way for 
      every cat or owner.
   c. Diet: y/d by Hill’s
      i. An extremely iodine-restricted diet that prevents thyroxine production.
      ii. Pros
          1. No pills, surgery, radiation, or hospitalization.
          2. Cats must be fed anyway so just change the diet.
          3. Controls intrathoracic tumors and those in ectopic tissue.
          4. Reversible.
      iii. Cons
          1. Must be fed exclusively – 100%!
a. Many hyperthyroid cats live in multicat households, so all may have to be fed y/d.
2. Expensive
   a. Even more so if a multicat household.
3. Not every cat will eat it.
4. Not every cat that eats it initially will do so long-term.
5. Not every cat responds (compliance failure?).
6. We do not know the results of long-term iodine restriction.
7. We do not know the long-term effect on euthyroid cats.
8. It is not a cure so thyroid carcinoma is still possible.
9. The withdrawal period before giving radioiodine is not known.

d. Methimazole/Tapazole®/Felimazole®
   i. Pros
      1. Prevents production of thyroxine so the disease is controlled.
      2. The least expensive initially.
      3. Reversible.
      4. Often best for 18+ year old cats.
      5. Often best for semi-loved cats.
   ii. Cons
      1. The adenoma continues to grow.
         a. 20% are carcinomas in 4 years.
         b. Rechecks with likely dose adjustments are needed every 3-6 months.
      2. Side-effects: 15-20% of cats
         a. Gastric irritation causing vomiting and anorexia.
            i. Begin with ½ dose for 4 days then go to the full dose.
            ii. Give enteric-coated tablets (Felimazole)
            iii. Transdermal application
               1. Greasy ears
               2. Contact dermatitis
               3. Expensive
         b. Hepatotoxicity
            i. Often fatal
            ii. Always do LEs prior to methimazole so you have a base line for comparison
               1. Hyperthyroidism will elevate LEs.
         c. Facial excoriation
         d. Peripheral lymphadenopathy
   3. The cat must be treated daily.
   4. The cat must be treated long-term.
   5. Rechecks and mediation costs make it more expensive than surgery or radioiodine after 2-3+ years.

e. Thyroidectomy
   i. Pros
      1. It is a cure. It removed the adenoma.
      2. Only requires one-night hospitalization.
      3. If unilateral, it is usually less expensive than radioiodine.
   ii. Cons
      1. There is a surgical/anesthetic risk.
      2. Hypocalcemia
         a. If all four parathyroid glands are removed.
            i. Expensive to treat.
            ii. May require long-term treatment.
            iii. Can be fatal.
      3. Should stabilize with methimazole first.
      4. Severing of the recurrent laryngeal nerve possible, especially when the adenoma is very large.
5. If bilateral, requires two surgeries to minimize side-effects.
6. An intrathoracic tumor may be missed.
7. Tumors in ectopic tissue may be missed so the disease continues following surgery.

f. Radioiodine (also known as $^{131}$I, $^{131}$I, and Radioactive Iodine)
   i. Pros
      1. It is a cure; it ablates the adenoma(s).
      2. Only requires one treatment.
      3. Treats all adenomas even if they are intrathoracic or in ectopic thyroid tissue.
      4. No side-effects.
      5. Can treat thyroid carcinoma (with about 5X dose) – but results in permanent hypothyroidism.
   ii. Cons
      1. Hospitalization required for about 4+ days (Texas regulation).
         a. This is a deal-breaker for some clients.
      2. “Anti-nuke” clients are averse.
         a. Some philosophically opposed to radiation.
         b. Some fear side-effects of radiation therapy because they are not properly informed.
      3. The most expensive initially.
      4. The dose calculation is imprecise.
         a. Undertreatment: the adenoma is still present and functional.
         b. Overtreatment: creates hypothyroidism.
      5. Not reversible.
      6. For two weeks after release from the hospital: (Texas regulations)
         a. Must scoop litterbox daily and take waste outside.
         b. Not around anyone < 18 years old.
         c. Not around anyone pregnant.
         d. Limited contact with owners.

g. My Recommendations
   i. Methimazole for: easily pillable cats; cats 17+ years old; owner with limited funds. Note: the cost is usually much higher if a transdermal form is used.
   ii. y/d: non-pillable cat; 17+ years old; not a picky eater; can be fed individually, or the owner has one cat, or the owner can afford feeding multiple cats.
   iii. Thyroidectomy: unilateral disease; cost conscious owners; young children or pregnant woman in the household; owner is nuke-averse; surgeon is available; radioiodine in not nearby.
   iv. Radioiodine: owner wants and can afford the Gold Standard treatment, Reasonably available

h. Tapazole Test
   i. Treat with methimazole until the TT4 is normal and determine the renal function at that time.
   ii. Indications
      1. Cats on y/d or methimazole.
         a. Check the renal values after 2-4 weeks (when the TT4 is normal).
      2. All cats before thyroidectomy or radioiodine.
         a. Mark Peterson says: Hyperthyroidism must be controlled or cured regardless of renal function.
         b. What if the renal values go up significantly during the TT?
            i. Treat for chronic renal disease.
      3. Cats with Red Flags
         a. 15+ years of age.
         b. TT4 = 15+
         c. The creatinine is inappropriately low.
d. Pre-existing CKD is present.
   i. PCV < 30%
e. If so, begin an ACE-I 1 week before RX and for 1+ months thereafter.

IX. If Charlie was your patient, what would your recommendation be?
   a. Control vs. Cure
   b. Y/d
   c. Methimazole
   d. Thyroidectomy
   e. Radioiodine

X. Eight days after treatment with radioiodine
   a. Creatinine = 6.8
   b. BUN = 91
   c. Phosphorus = 7.2
d. Diagnosis: IRIS stage 4
   i. Acute or Chronic?

XI. Treating Chronic Kidney Disease in Cats
   a. Chronic Kidney Disease: Canine vs. Feline
      i. Canine Model: death is at midnight; creatinine becomes abnormal at 11:00 PM
      ii. Feline Model: death is at midnight; creatinine becomes abnormal at 7:00 PM
      iii. ‘Early diagnosis’ in cats can occur much earlier than ‘early diagnosis’ in dogs using common tests found in a CBC and chemistry profile.
   b. Urine Specific Gravity
      i. Cats concentrate urine better than dogs. A non-dehydrated cat can have a USG of 1.085.
      ii. Many cats in early stage 2 have USG > 1.025.
      iii. Therefore, USG is not as sensitive in cats with early CKD vs. dogs with early CKD.
   c. Proteinuria: Leakage of protein into the urine is an early indicator of renal disease
      i. Microalbuminuria (MA)
         1. 1-30 mg/dl is abnormal; this range cannot be detected by a urine dipstick.
         2. Abnormal: 3+ positive tests at least two weeks apart.
         3. It can be elevated by CKD, urinary infection, urinary inflammation, metabolic disease, neoplastic disease
         4. Therefore, is specificity for CKD is low.
      d. Urine Protein: Creatinine Ratio (UPC)
         i. < 0.2: Normal
         ii. 0.2-0.4: Borderline
         iii. >0.4: Abnormal
         iv. High sensitivity and specificity.
   d. Next Steps: If either MA or UPC is abnormal, look for the cause of the renal disease with ...
      i. History
      ii. Physical examination
      iii. Blood pressure
      iv. CBC
      v. Chemistry Profile
      vi. Electrolytes
      vii. Urinalysis
      viii. Urine culture
      ix. Urinary imaging (radiographs and ultrasound)
      x. Kidney biopsy
      xi. Is an extensive workup justified in a cat with IRIS stage 2 disease?
   e. The IRIS Classification of Feline Chronic Kidney Disease
      i. Based on creatinine values

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<tr>
<th>Stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Azotemia</td>
<td>None</td>
<td>Mild</td>
<td>Mod</td>
<td>Severe</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&lt;1.6</td>
<td>1.6-2.8</td>
<td>2.9-5.0</td>
<td>&gt;5.0</td>
</tr>
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</table>
ii. Stage 2 straddles traditional “normal” and “abnormal” creatinine values

iii. Stage 4 is what we used to call Renal Failure. RF is an obsolete term for chronic disease.

iv. Modifications
   1. Stage 2a: Creatinine = 1.6-2.1 mg/dl
   2. Stage 2b: Creatinine = 2.2-2.8 mg/dl
   3. Stage 4a: Creatinine = 5.0-8.9 mg/dl (adjusted for muscle wasting)
   4. Stage 4b: Creatinine = 9.0+

v. Amer J Vet Res; 2001;62:375-383: “Administration of benazepril was also associated with … an increase in whole kidney GFR. Benazepril may be an effective treatment to slow the rate of progression of renal failure in cats with renal disease.”

vi. Beneficial Effects of Benazepril per Novartis to Canadian FDA-equivalent: 1) Inhibits RAAS, 2) Dilates the glomerular efferent arteriole, 3) Reduces glomerular pressure (renal hypertension), 4) Decreases protein loss, 5) Increases GFR, and 6) Increases the removal of creatinine and urea.

vii. Proceedings, State of the Art in Renal Disease in Cats and Dogs, Nice, FR 2007: “Is proteinuria simply a marker of CKD that is more likely to be rapidly progressive or does proteinuria cause progression of renal injury? If the latter is true, treatments that attenuate proteinuria are likely to be renoprotective and improve survival. Another possibility is that intraglomerular hypertension is a major cause of progressive renal injury in CKD and that proteinuria is simply a consequence of this intraglomerular hypertension.”

viii. Dose of benazepril and enalapril: 0.5-1.0 mg/kg q24h PO

ix. Potential side-effects
   1. Causes hyperkalemia.
   2. Causes hypotension in cats that are not hypertensive.
   3. Induces or worsens azotemia.

g. Calcitriol
   i. For an in-depth discussion: Dr. Nagode’s lecture on VIN  
   ii. Effects
      1. Increases blood calcium level by
         a. Increasing resorption in the kidneys
         b. Increasing calcium mobilization from bones.
      2. Prevention of renal secondary hyperparathyroidism (RSHPT)

Kidney disease ➤ ↓ Calcitriol & ↑ P ➤ Ca:P < 2:1 ➤ ↑ PTH ➤ RSHPT ➤ ↑ Ca ➤ Renal calcification ➤ Kidney failure

h. Goal of therapy: Prevent the onset of RSHPT, because it is VERY difficult to reverse.

i. To do so: replace calcitriol before the parathyroid cascade begins. Renal production of calcitriol begins when the creatinine becomes abnormal or earlier. Therefore, begin calcitriol as soon as renal disease is detected.

j. Response to calcitriol: Increased appetite, weight gain, more alert and active, increased longevity.

k. Twice weekly dosing required if:
   i. Phosphorus is > 6.0 OR
   ii. Hypercalcemia is present OR
   iii. If iCa cannot be performed.

l. If P > 6.0
   i. Feed a low P diet (protein restricted)
   ii. Add a phosphate binder to the diet or give orally with food.
      1. Aluminum hydroxide
         a. Conseal-AIH (www.bockvetpharma.com)
         b. Powder: Letco Medical; USP grade powder: www.letcomedical.com
            i. 500 gm for $55 + shipping.
            ii. Mix in canned food or “shake in a baggy” with dry food.
iii. Dose for 5 kg cat: Rounded ¼ teaspoon BID in food
iv. Dose may be doubled to reduce serum phosphorus to < 5.0 mg/dl.
v. A 2-month supply fills a 26-dram prescription vial.
c. Phos-Bind, www.RXVitamins.com; 1 scoop = 500 mg

2. Calcium-containing binders will routinely cause hypercalcemia
   a. Calcium acetate (PhosLo)
   b. Calcium carbonate (Epakitin)

m. If hypercalcemia is present
   i. Needs to be verified with ionized Ca
      1. Commercial labs or i-STAT1
      2. If iCa is normal, OK to begin daily calcitriol.
      3. If up to 1.6, proceed but must be twice per week schedule.
   4. Pat Schenck, DVM, PhD: The blood pH is helpful on a few levels. First, pH should be within a fairly tight range physiologically, so it's expected to be about 7.4 unless there is some metabolic derangement. If you get a reading on a sample and the pH reads >7.6, then that is very indicative that the sample has been mixed with air usually by shaking, and the iCa will be falsely low because of the higher pH. Air mixes with sample, CO2 increases, pH increases, proteins bind to calcium (alkalinity favors binding), protein-bound Ca increases, and iCa decreases (because the proteins in the sample have pulled iCa out of the sample and have bound to it). So, the iCa in those instances is inaccurate. It is best to be able to report the 'true' iCa concentration, but most hospital labs will employ an iCa correction to a pH of 7.4 (this is built into the analyzer). The correction to pH 7.4 gives a normalization of all iCa measurements to the same pH and eliminates the potential for various amounts of air contamination.
        a. Bottom Line: When running iCa on an iStat, look at the pH on the same sample. If it is > 7.5, the sample likely will have an iCa that is falsely lowered by air mixing in the sample. If the pH is ~7.4 (or slightly less), the sample can be considered valid.
   ii. Treating hypercalcemia
      1. Prednisolone: 1.1-2.2 mg/kg q12h PO
      2. Alendronate (Fosamax): 10 (~30) mg q7d PO.

n. If not iCa is available
   i. An expensive test if done commercially.
   ii. Routine chemistry machines will not perform it.
   iii. i-STAT1 permits it to be done cheaply and on-site in about 10 minutes.
   iv. The iCa value can be validated by looking at the pH (on the same test cartridge); it should be less than 7.5. A value of 7.5 or more indicates air contamination.

o. If we begin calcitriol at the onset of renal disease, when does renal disease begin?
   i. When the creatinine is elevated, which means 75% loss of function.
   ii. But, IRIS stage 2 begins at a creatinine of 1.6.
   iii. THE QUESTION: Have we properly defined “the normal creatinine values?”
   iv. At what age does IRIS stage 2 typically begin?
      1. Based on Norsworthy’s survey of 150 cats, ~30% of cats ages 2-5 and ~40% of cats ages 6-9.
   v. This is how I explain it to clients: See Client Handout below.
   vi. SDMA (symmetric dimethylarginine)
      1. Detects kidney disease when ~40% of function is lost.
      2. Included on IDEXX chemistry profiles.
      3. Individual testing: $19.95; 1 ml of serum
      4. Not affected by muscle loss, by liver, Cushing’s or heart disease, or by diabetes.
      5. Not influenced by hemolysis, icterus, or lipemia.
   vii. SDMA and Creatinine Comparison
2. The creatinine reaches 1.6 mg/dl when the SDMA reaches 15 µg/mL.
3. The onset of IRIS stage 2 is a creatinine of 1.6 and an SDMA of 15.

viii. The Mid-Life Screen
   1. I recommend beginning at age 6 years.
   2. A creatinine of 1.6 or an SDMA of 15 says: “Start calcitriol now.”

p. Dosing Calcitriol
   i. A study published in 1993 showed that calcitriol caused frequent hypercalcemia and renal calcification. However, the dose was too high: 6 ng/kg q24h (2.5X the current dose).
   ii. Current dose: 2.5 ng/kg q24h PO OR 9 ng/kg q3-4 days (2X per week)
      1. To avoid several problems and to increase compliance, I recommend twice per week dosing for all cats.
   iii. Compounding
      1. Most compounding pharmacies will make it, but efficacy is in doubt. Because it is preventing RSHP, it will be years before we will know about efficacy.
      2. Pharmacies known to prepare it correctly
         a. Roadrunner Pharmacy; 877-518-4589 (My preferred source.)
            i. Client pays you and you pay the pharmacy. This allows you to set the retail price. The pharmacy will not quote a price to the client.
         b. US Compounding; 800-718-3588
         c. Both have a license in every state, which is required.
   iv. Roadrunner Dosing: Every 3-4 days (Client pays you; you pay Roadrunner.)

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<th>Concentration</th>
<th>ml/dose</th>
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<td>up to 7.0</td>
<td>100 ng/ml</td>
<td>0.25</td>
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<tr>
<td>7.0-9.9</td>
<td>100 ng/ml</td>
<td>0.4</td>
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<tr>
<td>10.0-12.9</td>
<td>200 ng/ml</td>
<td>0.25</td>
</tr>
<tr>
<td>13.0-17.9</td>
<td>200 ng/ml</td>
<td>0.3</td>
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<tr>
<td>18+</td>
<td>200 ng/ml</td>
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1. US Compounding Dosing: Every 3-4 days

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<tr>
<th>Weight #</th>
<th>ng/dose</th>
<th>ml/dose</th>
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<td>0-5</td>
<td>16</td>
<td>0.25</td>
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<td>0.25</td>
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<tr>
<td>21-29</td>
<td>96</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Note that the concentration changes with each increment, but the volume remains constant.

v. Important
   1. Do not refrigerate or freeze because the oil congeals.
   2. When warmed, it will not disperse evenly again.

vi. Rechecks
   1. At 1 month of calcitriol: BP + iCa
   2. Every 3 months thereafter
      a. Kidney panel + PCV/CBC
      b. iCa every other recheck (q6m)
      c. BP once per year
   3. Every 4-6 months
      a. Clients $ limited
      b. Cats < 10 yrs. old and Stage 2a (1.6-2.1 mg/dl)

vii. PTH Testing
1. The Ideal
   a. Test before calcitriol is started as a baseline (but treat even if it is normal).
   b. Test at 1, 3, and 6 months of treatment to be sure PTH is decreasing or remains normal.

2. The Realities
   a. Our Cost: $115 + specimen prep and shipping.
   b. Cost to client for each test: ~$250??
   c. Reliability of the test
      i. Likely understates the true value.

q. Renal Diet
   i. Why a low protein diet?
      1. Old cats are less active, so they need less protein.
      2. Excess protein consumed is eliminated through the kidneys.
      3. The kidneys work harder.
      4. The kidneys wear out sooner.
   ii. Why are “renal diets” low in protein?
      1. Brenner Hypothesis promoted low protein diets for humans with renal disease; 1982
      2. Barry M. Brenner, MD
      3. Was controversial in 1982
      4. Still controversial
      5. Then, the pet food manufacturers adopted this approach.

r. The rationale for low protein diets has been questioned for many years.
   i. “Factors other than protein and calorie intake must be considered potential causes of progression of renal failure in cats. Results raise questions about the practice of restricting quantity of protein in the diets of cats with chronic renal failure, with the intention of ameliorating development of further renal damage.” Am J Vet Res; 1998;59:575-582
   ii. Dr. Deb Zoran: Says that “Old cats are less active, so they need less protein.” Is not true.
   iii. Dr. Deb Zoran, The Feline Patient, 5th Ed.: “The natural diet of cats in the wild is meat-based (i.e., rodents, birds, insects, small mammals), and, as such, cats are metabolically adapted to utilize protein and fat preferentially as energy sources without the need for or ability to utilize effectively dietary starches. The evolutionary differences of these obligate carnivores mandate cats to use protein for maintenance of blood glucose levels and as an energy source even when sources of protein in the diet are limiting or sources of CHO are present in the diet. The significant difference in protein requirements observed between cats and omnivores, such as dogs, illustrates this important metabolic distinction. More importantly, when protein is limited in the diet, cats will immediately use muscle tissue from their body to meet their protein and amino acids needs.”

s. Why avoid low protein diets?
   i. Emaciated old cats have palpable spine and pelvic bones due to protein depravation.
      1. Increasing caloric intake by increasing carbohydrates does not stop muscle wasting.
      2. High carb diets will cause weight gain, but it will be abdominal fat and not muscle.
   ii. Protein digestion declines with age. The typical 12-year-old cat only digests 75% of the protein it consumes.
   iii. Feeding a low protein diet to old cats can result in severe protein deprivation and muscle wasting, especially if they do not eat well.
   iv. Don’t forget that dogs are omnivores, and cats are carnivores.

t. Cat Food Labels
   i. Protein is the most expensive ingredient in a cat food.
   ii. However, the government only requires that the crude protein amount be listed on the label.
iii. But, crude protein is not the equivalent to digestible protein.
iv. We have not way to determine digestible protein or protein digestibility from the label.
u. Discrepancy between the use of lean body mass or nitrogen balance to determine protein requirements for adult cats. J Fel Med Surg, August 2013.
   i. Protein need is determined by nitrogen balance for AAFCO standards.
   ii. “Animals, including cats, can adapt to low protein intake and maintain nitrogen balance while depleting lean body mass.”
   iii. “Current AAFCO and NRC standards for protein adequacy may not provide adequate protein to support LBM. The minimum daily protein requirement for adult cats appears to be at least 5.2 g/kg, well in excess of current AAFCO and NRC requirements.”
v. Protein Digestibility
   i. Not stated on the label of grocery store or therapeutic diets.
   ii. Advise clients to call the manufacturer, but many will not divulge this information.
   iii. Determining digestibility requires extensive and expensive feeding trials that are not generally performed by small pet food manufacturers.
   iv. Most grocery store brands have 50-75% digestible proteins.
w. Most therapeutic diets have ~90% digestible proteins.
   i. Should have moderate protein for these cats instead of high protein.
   ii. There is a progressive decline in protein digestion at about 12 years of age. By 15, they are only digesting about 75% of what they eat.
   iii. Appetites are usually reduced, which reduces protein intake.
   iv. Norsworthy’s opinion of feeding traditional renal diets to cats in stage 4:
      1. If reasonably good muscle is present; not MCS of ¾ or 4/4.
      2. If the cat is eating VERY well.
      3. If significant WL is not occurring.
   4. If P cannot be controlled with a P-binder and a higher protein diet.
x. Renal diets: What to feed and when to start; Cailin R. Heinze, VMD, MS, DACVN; Medicine360; July 2016
   i. “Reducing dietary protein is probably the best known and most controversial nutritional modification for patients with renal disease. No evidence exists demonstrating that high-protein diets harm the kidneys per se.”
   ii. “Because most meats are high in phosphorus, the limiting factor in dietary phosphorus restriction in commercial diets is often the animal protein content.”
y. Tailor Senior Pet Diet Recommendations to Promote Health; Julie Churchill, DVM, PhD, DACVN
   i. “Protein requirements [of older cats], meanwhile, can be up to two times what the young adult animal might need, because protein turnover increases as a pet ages. It may be unrealistic to expect to increase lean muscle mass in a senior pet, but maximizing dietary protein quality and quantity in healthy seniors can maintain lean mass and help support the pet’s active life while promoting fitness and joint health.”
z. The Unique Metabolic Adaptations and Nutrient Requirements of the Cat; Beth Hamper, DVM, PhD, DACVN; August’s Consultations in Feline Internal Medicine, Volume 7.
   i. “It seems that nitrogen balance is an inadequate marker for determining optimal protein requirements and that veterinarians may not be recommending optimal dietary protein levels for cats. In the wild, cats have been found to tolerate high levels of protein in their diet. Average protein levels in feral cat diets as expressed on a dry matter basis are 63%, which is higher than any current commercial cat food.”
   ii. “The dietary protein requirement for the kitten is approximately 1.5 times the dietary protein requirement for the puppy. In contrast, adult cats require two times more protein than adult dogs and four times more protein than an omnivore, such as the rat (Table 62-1). The increased protein requirement in the cat is not for increased levels of essential amino acids but rather a dietary source of nitrogen.”
   aa. Purina’s NF Feline Early Care
      i. Moderate amount of high-quality protein.
      ii. Restricted phosphorus to help nutritionally manage cats with CKD.
iii. Contains EPA, an omega-3 fatty acid, to help reduce inflammatory mediators.
iv. Controlled sodium.

v. Added B-complex vitamins and potassium to help compensate for loss secondary to polyuria.
vi. Formulated to be non-acidifying.


XII. Hypertension

a. Incidence
   i. Incidence in IRIS stage 3 is 20-30%.
   ii. You should perform a blood pressure check on all cats in stages 2, 3, and 4.
   iii. Most stage 2 and 3 cats will hypertension will be asymptomatic at the time CKD is diagnosed.

b. Definition
   i. Somewhat controversial because of testing inconsistencies.
      1. Systolic < 160: Normal
         a. Treat if retinopathy, seizures, or stroke-like signs.
      2. Systolic > 200: Hypertension
         a. Treat all unless extremely stressed at the time.
      3. Systolic 160-180: May be stress related
         a. Treatment is a judgment call. Factor in stress. Ask about seizures and stroke-like signs; examine retinas for hemorrhage or detachment.

c. Getting Reliable BP Readings
   i. Quiet environment: exam room instead of treatment room.
   ii. Gentle restraint.
   iii. Have the owner present.
   iv. Do 2-3 readings; if fairly consistent, average them; if widely divergent, do to more readings and reject the highest and lowest.
   v. Have the heart and the artery tested on the same horizontal plane.
      1. Differences were detected at different sites. The hind limb readings were about 15 points higher than the front limb readings.
      2. Message: Take your readings at a consistent location.

d. Equipment
   i. All have pros and cons and a short learning curve.
   ii. Types: Doppler and Oscillometric
      1. Measuring level of agreement between values obtained by directly measured blood pressure and ultrasonic Doppler flow detector in cats; J Vet Emer & Crit Care; 2014;24(3):272-278.
         a. “Conclusions – Results suggest poor agreement between Doppler values and directly measured blood pressures in anesthetized cats. Use of Doppler in cats could be misleading and readings should be interpreted with caution in a clinical context.”
         a. “None of the 3 veterinary-specific oscillometric blood pressure units could be recommended.” Cardell Max 1, pet Map, HDO
         b. But, the HDO was not connected to a computer so its main advantage was not used.
         a. “The data support that the HDO is the first and only validated non-invasive blood pressure device and, as such, it is the only non-invasive
reference technique that should be used in future validation studies.”

e. Treatment Options
   i. Nitroglycerin paste: ¼” on ear q12h for 24-48 hrs.
   ii. Amlodipine (Norvasc)
      1. Have compounded; at 1 mg/ml give 0.6 ml initially and then to effect.
      2. Check the BP q2-3 days until < 160 mmHg.
   iii. ACE-i (benazepril or enalapril)
      1. Not as effective as amlodipine but can be combined with it.

f. Treating Asymptomatic Cats
   i. Put stage 2b or higher cats on an ACE-I at the time of diagnosis of CKD.
   ii. Recheck the cat in 4-6 weeks and include a blood pressure determination.
   iii. If elevated, add amlodipine
      1. 0.6 mg/cat initially.
      2. Adjust q2-3 days to response.
   iv. If the cat does not have CKD but is hypertensive: use amlodipine only.

g. Treating Symptomatic Cats
   i. Retinopathy/Encephalopathy
      1. Nitroglycerin (for 48 hrs) + amlodipine + ACE-i
   ii. Focal retinal hemorrhage only
      1. Amlodipine + ACE-i
   iii. Severe retinal hemorrhage/hyphema
      1. Nitroglycerin (for 48 hrs) + amlodipine + ACE-i

XIII. Erythropoietin Replacement
a. Renal anemia
   i. Feline RBC’s live ~70 days; some must be replaced each day.
   ii. Erythropoietin, made exclusively in the kidneys, stimulates the bone marrow.
   iii. CKD results in anemia because erythropoietin production falls so bone marrow
       stimulation stops or is greatly reduced.

b. When to use
   i. PCV < 25%: probably treat.
   ii. PCV < 20%: definitely treat.
   iii. Restoring normal PCV increases appetite and activity level.

c. Erythropoietin (Epogen, Procrit) can be given by injection.
   i. Being of human origin protein, 15-20% of cats develop antibodies to it.
   ii. Those antibodies destroy Epogen/Procrit and erythropoietin made in the kidneys.
   iii. The cat becomes “transfusion dependent.”

d. Darbepoietin (Aranesp) is a synthetic product that is MUCH less likely to cause antibody
   production.
   i. It is more expensive than Epogen or Procrit, but it is given less frequently.
   ii. Dose: 1-2 µg/kg weekly for 2-4 weeks then q2-4w. (approx. 0.2 ml per dose)
   iii. Treatment cost is about the same.
   iv. Availability is more reliable with darbepoietin.

e. When to use
   i. PCV < 25%: probably treat.
   ii. PCV < 20%: definitely treat.

XIV. Appetite Stimulation
a. Famotidine (Pepcid): 2.5 mg q12-24h for gastric hyperacidity
b. Cyproheptadine: 2 mg BID: appetite stimulant
   i. Takes about 15 minutes for effect; lasts about 15 minutes

c. Vitamin B12: appetite stimulant; can be given alone or in SC fluids

d. Benazepril: main side effect is appetite stimulation, but not profound

e. FortiFlora (Purina): Probiotic for diarrhea but often results in better appetite

f. Mirtazapine: 2 mg q24-72h; appetite stimulant
   i. Can be given q24h if renal function is normal.
   ii. Compounding required to get dose this low.
   iii. Side effects (even at the appropriate dose in a few cats)
1. Nervousness/hyperactivity
2. Vomiting
3. Vocalization (pain?)
4. Arrhythmias

XV. Giving Pills to a Cat
   a. Do a Pilling Demo
      i. To determine feasibility in this cat.
      ii. To educate the owner on technique.

XVI. Central Venous Catheterization
   i. Advantages over short (cephalic) catheters
      1. Can be left in place for up to 7 days.
      2. Blood can be collected through them for analyte testing.
   ii. Recommended: Mila International; Long Line Kit; LL 2045
      1. Placed in medial saphenous vein.
   iii. AniSet Anti-Kink IV Set; www.millpledge.com; cost about $0.75 more than conventional IV sets but MUCH less likely to stop flowing due to kinking.

XVII. In-house Blood Testing
   i. Advantages
      1. Takes < 15 minutes to get results. During that time I go to another exam room.
      2. If additional treatments are needed, the client can walk out with the new meds in hand. Having to come back another day reduces compliance.
      3. Having to make a phone call the next day with results makes it difficult for me to recall the details of the case.
   ii. A Desirable Chemistry Machine
      1. Requires a sample size on more than 0.5 ml so you do not contribute to or cause anemia.
      2. Needs to perform the needed tests in 15 minutes
         a. Creatinine, BUN, P, K, TCO₂, Ca + PCV or CBC
      3. The i-Stat is used to determine ionized calcium in less than 10 minutes with the same sample.

XVIII. Client Motivation
   i. What are the important factors that determine whether an owner will treat a chronic disease on a long-term basis?
      1. Love for Pet
      2. Pet’s Age
      3. Pet Pain
      4. Life Quality
      5. Cost-Related
      6. Survival Chances
      7. Discussed with Others
      8. Veterinarian

Take Home

- Redefine “abnormal” creatinine: Stage 2 begins at 1.6 mg/dl (SDMA of 15)
- Do annual blood screens at 6+ years of age.
  - 40% of cats < 10 yrs. old will be in Stage 2
  - 60+% of cats > 10 yrs. old will be in Stage 2
- Begin treating at Stage 2
  - Creatinine = 1.6-2.1: Calcitriol (Roadrunner Pharmacy) + NF Early Care (Purina)
    - 1.6 = 40% loss of nephron activity
  - Creatinine = 2.2+: Add benazepril (generic)
    - 2.2 = 75% loss of nephron activity
• Others: PRN (phosphate binder, K supplement, SC fluids, darbepoietin, amlodipine, appetite stimulants)

  Do blood testing in-house
  • Better compliance because results are available within 15 minutes.
  • Machines needed: Hematology, Chemistry Analyzer with Electrolytes, iStat

• Recheck, recheck, recheck
  • Recall system essential.
  • After one month on calcitriol
    ▪ Blood pressure (if not previously performed).
    ▪ iCa
  • Each 3 months thereafter
    ▪ Chemistry/Renal Profile
      ▪ Essentials: creatinine, P, K, BUN + PCV (CBC)
  • iCa: ~ every 6 months when on calcitriol
  • BP: ~ every 12 months if last BP was normal.
  • Rechecks OK every 4-6 months for cats in stage 2, for $ sensitive owners, for semi-loved cats.

• Get a sign to celebrate your 20+ year old patients!
Calcitriol for Cats with Kidney Disease

Calcitriol is a hormone produced in the kidneys. Its production falls to nearly zero when the cat has kidney disease. It is used to prevent Renal Secondary Hyperparathyroidism (RSHPT).

RSHPT is a mouth-full to say, a mind-full to remember, but a very important complication of kidney disease that needs to be prevented. Here are eight steps that summarize how it affects the cat.

1. We consider kidney disease to be present when about 40% of kidney function is lost. It may last many months to a few years before kidney failure occurs and becomes life-threatening. It is usually documented and monitored with creatinine values. It can be confirmed with a test called SDMA.

2. Kidney disease results in two problems. First, calcitriol production drops to nearly zero. Second, the kidney loses its ability to move phosphorus (P) from the blood into the urine resulting in blood P levels that are too high.

3. The body needs twice as much calcium (Ca) as P in the blood. With an excess of P, the ratio drops below the desired 2:1 ratio.

4. When the body no longer has the ability to efficiently dump P into the urine (due to kidney disease), it seeks ways to fix the Ca:P ratio problem. If sufficient calcitriol is available, calcitriol solves the problem by increasing the Ca level. However, it is not available in kidney disease. Therefore, the backup plan is to use the parathyroid gland to increase Ca levels. It increases production of parathyroid hormone (PTH), the agent that stimulates the parathyroid gland.

5. Prolonged increased PTH production overstimulates the parathyroid glands resulting in an increase in its size and function. This is called Renal Secondary Hyperparathyroidism.

6. The increase in parathyroid function removes Ca from the bones, increases absorption of Ca from the intestines, and inhibits the kidneys from releasing Ca into the urine. These changes shunt Ca to the blood to fix the Ca:P ratio problem. Simply put, if the body cannot decrease the blood P level, it solves the problem by increasing the blood Ca.

7. Although an increase in Ca in the blood solves the immediate problem of a low Ca:P ratio, the enlarged and overstimulated parathyroid glands are now functioning without a control system to tell them when they need to slow down or stop. This results in too much Ca accumulating in the blood. As a result, Ca is laid down in tissues throughout the body, most notably in the kidneys. Eventually, excessive Ca in the kidneys causes calcification of kidney tissue. These Ca deposits clog the kidneys’ filtration system.

8. Calcification results in declining kidney function leading to life-threatening kidney failure.
In summary, RSHPT worked to solve one problem (lack of enough Ca in the blood), but it resulted in another (kidney failure). Instead of helping the cat, the end result is harm to the cat.

The ongoing problem with RSHPT is that the body has no way to turn off hyperfunctioning parathyroid glands. The enlarged parathyroid glands continue pulling Ca out of the bones and laying it down in tissues throughout the body. Thus, we need to prevent RSHPT from happening. That is where calcitriol comes in.

Calcitriol raises blood calcium levels without stimulating the parathyroid glands. It prevents the parathyroid gland from making increased PTH and becoming overstimulated. However, it needs to be given BEFORE parathyroid overstimulation occurs. Thus, calcitriol needs to be started early in the courses of kidney disease. It is best started when the blood Ca and P levels are still normal.

If the blood level of P is elevated at the time kidney disease is detected, it must be controlled with a drug called a phosphorus binder. This drug is put in the food or taken orally. It binds to the phosphorus in the food so P is not absorbed into the body. Instead, excess P is passed in the stool. If your cat already has an elevated P level at the time of diagnosis, or if the P elevates during the course of treatment, a phosphorus binder is started. It will usually have to be given long-term.

Calcitriol should be started as soon as kidney disease is detected. There are several factors in this determination, but creatinine values are a very important part of that decision.

Calcitriol may be given on a daily schedule or on a twice per week schedule. If Ca and P levels are normal, we recommend whichever schedule works best for you and your cat. However, when the P level or the Ca level is too high, calcitriol must be given twice per week. When these problems are resolved, it can be continued on a twice per week schedule or given on a daily schedule.

Calcitriol is made in different concentrations based on the cat’s body weight and whether or not you are giving it daily vs. twice per week. IT IS VERY IMPORTANT NOT TO USE THE SAME PRESCRIPTION (CONCENTRATION) BETWEEN DAILY AND TWICE PER WEEK SCHEDULES. ONLY GIVE IT AS DIRECTED ON THE PRESCRIPTION LABEL. If you wish to change from one schedule to another, a new prescription will be needed.
Screening for Early Kidney Disease

For many years, we have recommended an annual blood panel for cats 10 years of age or older. The most common abnormality found is early chronic kidney disease. Recent advances have made earlier blood screening successful in finding and treating kidney disease even before age 10. Now we are recommending that cats six years of age or older have annual blood screens. The Midlife Screen is for cats 6-9 years of age. (A cat at age six is equivalent to a human at age 45.)

Kidney disease is the number one killer of cats over 14 years of age. Although finding the disease at 10-12 years of age gives us a head start on treatment, finding it even earlier means that we can now add several extra years of quality life to thousands of cats. We now have the tests to find it when about 40% of function is lost. About 40% of cats ages 6-9 already have this ultimately fatal disease.

Progression of Kidney Disease

"Normal Creatinine" = 0.3-2.1

Average Age = 6.0 yrs.

40% Loss of Function

"Kidney Disease"

75% Loss

"Kidney Failure"

85% Loss

Important Kidney Facts

- Most older cats die from kidney failure if they do not develop another life-threatening disease.

- The kidney deterioration continues throughout the cat’s lifetime until the kidneys can no longer remove sufficient waste products from the blood to support life. This is called kidney failure.
- There are three points in the progression of kidney disease (deterioration) that we can reliably identify:

1) 40% loss of function. The creatinine value is about 1.6 mg/dl. Although this value is still in the “normal range” for creatinine, the kidneys are not normal. About 40% of cats ages 6-9 are affected.

2) 75% loss of function. The creatinine value first exceeds the high end of the normal range. The cat may appear normal; however, it often has mild weight loss and an increase in thirst and urination. The most easily identified sign is more wet litter in the litter box.

3) 85% loss of function. The creatinine is about 5.0 mg/dl. The cat is losing weight, has a poor to decreased appetite, drinks and urinates excessively, experiences moderate to severe dehydration, and becomes progressively less active. Aggressive treatment in the hospital and at home is required if the cat is to improve. With treatment, some cats return to a fairly a normal state of health; however, the cat should not be expected to live more than a year. Many live only a few weeks.

**Treatment with Calcitriol**

Calcitriol (cal sa TRY ol) is our latest tool to slow the progression of chronic kidney disease. **Calcitriol is the active form of vitamin D; it is made exclusively in the kidneys until renal function declines.** Protocols for its use have been developed, and a recent study demonstrates its effectiveness in cats. The following is a summary of how it works to extend the life of your cat:

- The body demands a 2:1 ratio of calcium to phosphorus in the blood. There needs to be twice as much calcium as phosphorus.

- Phosphorus is found in all foods and is absorbed into the blood as the food is digested.

- If the phosphorus level gets too high, normal kidneys release the excess into the blood (Plan A). However, kidney disease prevents that from happening, resulting in too much phosphorus in the blood and an improper calcium to phosphorus ratio.

- Calcitriol is a hormone made by the kidneys that has a major role in calcium and phosphorus levels in the blood. It causes an increase in calcium in the blood (Plan B). However, calcitriol can no longer be made by the time there is 40% loss of kidney function. This occurs about age 6 years.

- Without calcitriol, the body goes to Plan C to fix the improper calcium to phosphorus ratio by raising the calcium level in another manner. The parathyroid gland is stimulated to fix the problem. It “fixes” it by removing calcium from the bones and moving it into the blood.

- Plan C fixes the problem in the short-term, but it ultimately results in uncontrolled production of parathyroid hormone causing too much calcium to accumulate in the blood.

- Excess blood calcium results in calcium deposited in various body tissues including the kidneys. This is called calcification and leads to a more rapid onset of kidney failure.

- In short, Plan C (also known as renal secondary hyperparathyroidism or RSHPT) initially is a good thing, but it ultimately results in severe damage to the kidneys. Once started, it cannot be stopped, so the kidneys decline at a faster rate.

- If given before Plan C (RSHPT) occurs, calcitriol can add 1-2 years of good-quality life to most cats with kidney disease.

Calcitriol is a preventive drug. It works best when started early in the course of kidney deterioration. Because it is a hormone made by the kidneys, it has no side-effects if it is dosed properly.
Chronic Small Bowel Disease in Cats

I. Overview

1. The Four Clinical Signs of Chronic Small Bowel Disease
   i. Chronic vomiting (2X/mo or more)
   ii. Chronic diarrhea (1+ mo duration)
   iii. Weight loss
   iv. Polypagia
      a. Compensatory
   v. Usually only 2 are present, usually chronic vomiting and weight loss
   vi. Many cats have weight loss ONLY.
   vii. If BW is normal in a WL cat, consider CSBD as the next differential.

2. Chronic vomiting is very common in cats, but we (veterinarians and owners) have either made excuses for it or accept it as normal using the following excuses:
   b. My cat has a nervous stomach.
   c. It is just hairballs, and they are normal.
   d. “He’s just a puker,” i.e., it is normal for this cat.

3. Most chronic vomiting and chronic diarrhea in cats originate in the small bowel, not in the stomach. Most commonly, chronic vomiting is a manifestation of small bowel disease.

4. What we are not talking about
   a. Vomiting of whole dry food is not due to eating too fast. Cats typically swallow 80% of the dry food they consume.
   b. Cats that eat grass vomit because grass is irritating to the stomach. They eat it because they like it.

II. The Differential List for Chronic Small Bowel Disease

1. Chronic inflammatory disease 48%
2. Neoplasia without mass formation 48%
   i. Small cell lymphoma
   ii. Large cell lymphoma
   iii. (Mast cell tumor)
3. Food intolerance/allergy 3%
4. Misc: infections, parasites. 1%

III. Terminology

1. Chronic enteritis or chronic inflammatory disease
   i. Chronic small bowel inflammation of any cause.
   ii. Inflammatory bowel disease: Inflammation of unknown cause.
   iii. The histopath will usually be the same for both.

IV. Diagnostic Approach

1. Blood panel to rule out hyperthyroidism, diabetes, and chronic renal disease.
   i. No blood test or tests to date can distinguish chronic enteritis vs. lymphoma.
   ii. Thyroid tests: It is said the hyperthyroidism causes chronic vomiting. That is possible, but most of these cats had CSBD and then became hyperthyroid.

2. GI Panel
   i. Cobalamin: lower small bowel disease.
   ii. Folate: upper small bowel disease.
   iii. But, the location is not specific for enteritis vs. lymphoma.

3. Ultrasound of stomach and intestines
   i. Look for thickening of the walls (2.8 mm or more)
   ii. Two main differentials
      a. Enteritis and lymphoma
      b. They have the same clinical signs and ultrasound findings.
      c. Differentiated by the pathologist.

4. Small intestinal biopsy
   i. Examine the entire 4 feet of the small bowel.
   ii. Take full-thickness biopsies of all 3 areas plus more if indicated.
iii. Via a laparotomy.
iv. Possible exception: food trial for 6+ weeks.

V. Segmental Disease
   1. Small bowel disease is segmental in over ¾ of cats. Areas of normal and abnormal alternate. It is important to examine the entire bowel to make proper biopsy site choices.

VI. Advantages of laparotomy/biopsy vs. endoscopic biopsies
   1. The small bowel is 4 feet long.
   2. CSBD is segmental so the entire small bowel needs to be subject to biopsy.
   3. Full-thickness biopsies.
      i. Allow the pathologist to see all layers of the bowel.
      ii. Produces a large amount of “readable mucosa.”

VII. Small bowel biopsy technique
   1. Small bowel
      2. You need a full-thickness sample.
         i. Cut out a wedge beginning on the antimesenteric side of the bowel.
         ii. Alternate: 6 mm biopsy punch (**Much better sample than a wedge made with a scalpel.)
         iii. Pathologist input: More tissue is better and the less the tissue is handled the better.
            a. Scalpel wedges often have minimal mucosa and the little that is present is traumatized.
            b. 4mm punch biopsies are so small that they are just put into the cassette and 4mm mucosa is readable per sample. However, often the edges are damaged.
            c. 6mm punch biopsy is large enough to bisect and put both halves on the block giving the pathologist 12mm of mucosa per sample and the edge artifact is minimal.
            d. Do the math: Scalpel 8mm incision = 1-4 mm traumatized mucosa. 4mm punch = 4 mm mucosa. 6mm punch = 12mm mucosa.
            e. A 6mm punch sample gives 3 times the readable tissue as a 4mm punch sample.
         iv. Trim away excess mucosa so you suture muscle and serosa to muscle and serosa.
      v. Use simple interrupted through-and-through sutures of 4-0 PDS placed 1 mm apart.
      vi. When the bowel is closed, test with a saline injection.
      vii. Consider biopsy of the mesenteric lymph node if it is enlarged, but that is not a part of my current protocol. It is often misleading as LN may be inflammatory with lymphoma in small bowel.

VIII. Pancreas Biopsy
   1. Examine both limbs of the pancreas. Biopsy an area that appears grossly abnormal. If there are no abnormal areas (likely), use a 4-mm biopsy punch to take a sample on the edge of the organ to avoid the centrally located exocrine duct; bleeding unlikely.
   2. Alternative Technique: Use a 4-mm biopsy punch to “scoop” pancreatic tissue from the surface or edge of the organ. As above, avoid the exocrine duct.
   3. If bleeding occurs, use a clotting powder (HemaBlock [formerly Bleed-X] Vet Clotting Powder, DVM Solutions)
   4. Because this is a very small sample, put it in a separate tube so it does not get lost during tissue processing.

IX. Liver Biopsy
   1. Cut a wedge of liver (1 cm on a side) with scissors then close with (usually) one 4-0 PDS suture. Choose an area that appears grossly abnormal, but most cats with liver disease have diffuse disease so the location is usually chosen based on accessibility. Do not crush this tissue during the biopsy process or when handling the tissue.

X. Biopsy sequence
   a. Remove the falciform ligament.
   b. Biopsy the liver.
   c. Biopsy the pancreas.
   d. Biopsy the duodenum.
   e. Examine the jejunum and the ileum from one end to the other.
f. Biopsy 2+ sites but at least one each of the jejunum and the ileum.
g. Check the pancreas and liver for bleeding.
h. Close the abdomen.

XI. Case Schedule
1. Day 1: Surgery
2. Day 2: Remove IV and feeds about 24 hours post-op.
3. Day 3: Discharge the cat.
4. Day 5-7: Get HP report, call owner with DX, send appropriate treatment document.

XII. Evidence is mounting that CSBD is a continuum of one disease.
1. Begins with mild inflammation of the small bowel, possibly within the first 2-3 years of life.
2. Progresses to severe inflammation known as IBD
   i. The pancreas and liver may also be involved: Triad Disease
3. Progresses to lymphoma: small cell, intermediate cell, large cell, large granular cell.
4. Evidence
   i. Age: IBD occurs in younger cats (even though there is a tremendous overlap of ages between the two).
   ii. The youngest cats we have diagnosed with small cell lymphoma are 6 years. The youngest cats with chronic enteritis are 2 years old. (N=600)
   iii. Cats are found with inflammation in the pancreas and/or liver but lymphoma in the small bowel. Was it Triad Disease that transformed in the small bowel? In some cases, very early lymphoma is found in the pancreas and/or liver.
   iv. Enteritis and lymphoma have been found in different parts of the same cat’s small bowel.
   v. PCR (PARR) testing is needed to differentiate enteritis from lymphoma in some cats.
   vi. Large cell lymphoma has been found at necropsy in cats histologically diagnosed with small cell lymphoma and treated. Treatment is often successful for several months then fails.

XIII. Hairball obstruction
1. Chronic small bowel disease (IBD or lymphoma) can cause reduced small bowel motility.
2. This results in slower movement of hair through the GI tract.
3. This results in more vomiting of hairballs or hairball obstruction.
4. When removing a hairball, biopsy the bowel about 3-4 inches aboral (downstream).
5. Expect to find that the cat has either chronic enteritis or lymphoma.

XIV. Norsworthy’s thoughts regarding hairballs
1. Hairballs can be normal due to normal shedding and the cat’s grooming behavior.
2. However, most chronic cases are a sign of chronic small bowel disease.
3. Therefore, ultrasound the small bowel.
4. If the US is normal, treat for hairballs – hairball diet, GI lubricants.
   i. If the response decreases over time, US the SI again.
5. If the US is abnormal, recommend surgery for small bowel biopsy.
6. Treating hairballs symptomatically can mask the signs of chronic small bowel disease. Our concern is allowing IBD to transform to lymphoma.
7. Treatment options
   i. Shave the cat’s hair every 3 months
   ii. Mineral oil – ONLY use it by putting it in the food.
   iii. Lubricants: Laxatone, etc.
   iv. Hairball diets
   v. Capilex: www.bockvetpharma.com; Chewable; Not available on the Internet.

XV. Histopathology Service
2. Texas Veterinary Pathology; (830) 237-2955; texvetpath.com
3. 3-4 small bowel samples: $70; 3-4 small bowel samples + liver + pancreas = $110; includes FedEx.
4. Ambiguous cases: IHC performed for an additional $70.

XVI. Publications

3. Diagnoses
   i. Normal 1%
   ii. Chronic enteritis 49%
   iii. Adenocarcinoma 1% |
   iv. Mast cell tumor 3% | --- Neoplasia 50%
   v. Lymphoma 46% |
     a. Large cell 15%
     b. Small cell 85%

XVII. Therapy
   1. General prognoses
      i. Good: food reaction, chronic enteritis, small cell lymphoma, mast cell tumor.
      ii. Less Good: large cell lymphoma, large granular cell lymphoma
      iii. Bad: adenocarcinoma.

XVIII. Therapy for Chronic Enteritis
   1. IBD is a diagnosis of exclusion. We must rule out known cause of chronic enteritis to justify a diagnosis of IBD. The histopath will be the same for the following. Eliminate each with therapy.
      i. Food allergy/intolerance: food trial
      ii. GI Parasitism (Tapeworms, Physaloptera, Ollulanus, and Giardia): Droncit injection + oral fenbendazole
      iii. Dysbiosis (bacterial overgrowth): metronidazole
   2. Note: The quantity when using liquid Panacur liquid is too great; get compounded capsules or liquid: 50 mg/kg q24h PO; Roadrunner Pharmacy: recommended chicken marshmallow flavor. Very bitter drug; the marshmallow masks the bitter taste.
   3. Note: Metronidazole: 50 mg compounded tablets q24h PO
   4. Note: Do not use a probiotic during a food trial.

XIX. Therapeutic trial schedule
   1. Day 1-42+: Food trial
   2. Day 1-5: Fenbendazole
   3. Day 6-36: Metronidazole
   4. Recheck at 6+ weeks to assess success or failure.
   5. Do not use steroids or do not use them past Day 30.

XX. Cobalamin (B12)
   1. Testing can be done (GI Lab, Texas A&M) OR treat every cat.
      i. 1000 mcg/dose
      ii. Give SC 2X per week for 6 weeks then
      iii. Give SC 1X per week for 6 weeks.
      iv. Advantage of treating all is that vitamin B12 is a good appetite stimulant, which is a plus when changing a cat’s diet.

XXI. Diet: Change to a low-carb, high-protein diet and feed long-term
   1. My preference: EN or DM.

XXII. Therapy for IBD
   1. Immune suppressants
      i. One of more of the following needed to suppress the over-reaction of the immune system. The goal is control not cure; therefore, treatment is needed long-term.
      ii. Corticosteroids: prednisolone 2 mg/kg q24h PO or Depo-Medrol at 20 mg q30d.
      iii. Oral pred preferred; less chance of inducing diabetes.
      iv. Alternatives if pred not effective.
         a. Cyclosporine (Atopica): 25 mg q24h PO for 15-30 days then 25 mg q48h PO. May change to prednisolone for long-term control.
b. Lomustine (CCNU):
   a. 6, 9, and 12 mg capsules q28d PO. See below.
      i. Monitor for neutropenia.
      ii. I use this if the wall thickening is great or there are eosinophils in
          the inflammation.
      iii. Give 2-3 doses with prednisolone or Depo-Medrol then continue
           with the steroid only.
   v. Probiotic: FortiFlora (Purina) or Proviable (Nutramax)

XXIII. Therapy for Lymphoma
1. Success is remission, not cure. Remission is defined as lack of clinical signs. These cats will
   stop vomiting, eat well, regain their lost weight, and become very active. The small bowel
   walls should return to normal or near normal as documented by ultrasound.
2. Short-term
   i. Vitamin B12: 1000 mcg/dose
      a. SC 2X per week for 6 weeks then SC 1X per week for 6 weeks
      b. May be given long-term if it increases the appetite and make the cat feel better.
3. Probiotic (FortiFlora or Proviable) for 30-90 days or long-term.
4. Vomiting control: Cerenia or transdermal metoclopramide.
5. Diet
   i. Low-carb, high-protein diet preferred
   ii. EN or DM (Purina)
   iii. Should be fed long-term.
6. Chemotherapy Options
   i. Prednisolone: 2 mg/kg q12h PO for +7-10 days then reduce slowly to 5-10 mg/cat q24h PO. Least expensive approach with fewest side effects; however, the least effective approach. If given alone for several weeks, the response to other chemo protocols may be reduced significantly.
   ii. Modified Wisconsin protocol: 15 treatments in 24 weeks using Modified CHOP (L-asparaginase, vincristine, cyclophosphamide, chlorambucil, doxorubicin, prednisolone); first remission rate 68%; median survival time 225 days. See The Feline Patient editions 2, 3, or 4 for specific protocol. The protocol of choice for most veterinary oncologists.
   iii. Chlorambucil + prednisolone: Chlorambucil (0.1 mg/kg q24h PO or 6-8 mg/m2 PO. The tablets should never be split so cats must take 2 mg q24h PO to q3d depending on the weight of the cat; Prednisolone (1-2 mg/kg q24h PO)
   iv. Lomustine + prednisolone

XXIV. Lomustine Protocol
1. Generally not considered a first-line chemotherapy agent. It is usually given as a rescue drug to
dying cats, so its efficacy is considered poor.
2. My treatment of choice for lymphoma (both) and mast cell tumors.
3. Lomustine: (CCNU): See dosing chart below
4. Depo-Medrol q4w (or oral pred at 1-2 mg/kg q24h PO)
5. Monitor for neutropenia. If it occurs, use the next lower dose of lomustine. If neutrophil count
   falls below 1.0, delay the next treatment until neutrophil count is at least 1.5 (~ 2 weeks). In
   Norsworthy’s experience neutropenia occurs about 40% of the time, and the prognosis seems
   to be better in these cats.
6. Dosing of lomustine
   i. Body Weight in Kg  Mg of Lomustine
      a. 2.0-3.0  6
      b. 3.1-4.5  9
      c. 4.6-5.9  12
      d. 6 or more 15

7. Other side effects
   i. Very slow regrowth of hair from surgery. (Very common)
   ii. Focal alopecia, any location (Uncommon)
iii. Pleural effusion; it is a grave prognostic sign. (Rare) Likely due to lymphoma in the myocardium.

8. Protocol:
   i. Visit 1: CBC + administer lomustine + give Depo-Medrol at the time of stitch removal = 10-14 days post-op.
      a. Also start vitamin B12, probiotic, LCHP diet.
   ii. Visits 2-6: Recheck, CBC, & lomustine 4 weeks later.
   iii. Visit 6: Repeat ultrasound: measure small bowel wall thickness.
      a. Success is remission, not cure.
      b. Vomiting stops
      c. Good appetite
      d. Weight gain (if weight loss initially)
      e. Good quality of life
      f. Small bowel walls normal or greatly improved.
      g. At 6th dose, explain that discontinuing lomustine will eventually result in relapse and that cats do not respond after relapse occurs. However, continuing long term results in permanent damage to the intestinal wall lining resulting in malabsorption.
      h. Measure the small bowel wall.
         a. If improved or normal and clinical signs are gone or much improved:
         b. Give 2-4 more doses at 6 week intervals + Depo-Medrol then stop.

XXV. Main messages
1. Chronic vomiting is VERY common in cats: 1/5 over 10 years of age.
2. It is so common that we have made excuses for it.
3. Therefore, clients usually do not report it.
4. You have to ask about chronic vomiting.
5. Chronic vomiting is not normal.
6. 99% of the time it originates from the small bowel, not the stomach.
7. CSBD is segmental in most cats.
8. Biopsies are needed in the proper locations, as determined by full bowel inspection.
9. Biopsies need to be in the correct locations and full-thickness.
10. You can do this, and you should do it.
11. You can treat these cats and you should treat these cats.
12. Your clients and your bottom line will appreciate it.
Increasing Acceptance of Laparotomies

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We averaged 2.1 laparotomies per week during 2012 through 2016. However, it took us four years to get to that level. See Figure 1. It took most of those four years to make the connection between “normal vomiting” and small bowel disease. After a few laparotomies with histopathologic confirmation of our suspicions, we became more and more confident that we would get an answer if we could just do the biopsies.

During those four years, we also learned to appreciate the segmentality of chronic small bowel disease (CSBD) and appreciate how important it is to have access to the entire small bowel so biopsies could be taken at the correct locations. Although endoscopic biopsies had been my primary approach to the vomiting cat, I realized the limitations (and folly) of getting a biopsy from 1-2 inches of duodenum when the small bowel in the cat is about four feet long.

How to Get Consent to do a Laparotomy

1. After nine years and 600 laparotomies we are absolutely convinced that a laparotomy to do multiple full-thickness biopsies of the small bowel and to biopsy the liver and pancreas is the correct way to diagnose cats with chronic small bowel disease and its associated diseases. That is the first step in getting clients to let me do surgery. I can speak with authority because the data is there. See references 1 and 2. Note that in the second paper we looked at ways, other than surgery, to differentiate chronic enteritis and lymphoma. We could not find a single way short of laparotomy that is reliable.

2. After the client admits that the cat vomits twice per month to daily, he or she will have one or more of four excuses: 1) The cat eats too fast. 2) The cat has a sensitive stomach. 3) The cat vomits hairballs and that is normal. 4) The cat is “just a puker,” i.e., it is normal for this cat. Without being confrontational, do not agree with these excuses. If you do, the discussion stops.

3. Owners are more likely to permit a laparotomy if they have visual evidence that a problem in the small bowel really exists. Watching performance of the ultrasound study is the best way to do this. Find a clearly visible loop of bowel and point out the lumen and the four wall layers. Note that the wall should be 0.25 cm or less in thickness. Also note that most cats have some normal measurements and some abnormal measurements (segmentality) so finding normal measurements does not rule out the presence of disease.

4. As the abnormal ultrasound findings become apparent, explain that thickened small bowel loops have two differentials: chronic inflammation (call it IBD) and lymphoma. IBD is much like Crohn’s Disease, and we do not know the cause of it or IBD. (What we are saying is, “If MDs do not know the cause of Crohn’s Disease, it is OK if DVMs do not know the cause of IBD.”) Both look the same on ultrasound, and both produce the same clinical signs.

5. State that if chronic enteritis is present, the walls will be packed with inflammatory cells. (This statement sets you up for needing to have the cells examined by a pathologist.) However, if lymphoma is present, the walls will be packed with lymphoma cells. (Don’t use the term ‘cancer’ at this point in the discussion.)

6. State that differentiation requires a microscopic examination of the small bowel walls by a pathologist, and the segmental nature of the disease requires that we get samples from the correct locations. These are determined after inspection of the entire intestinal tract.

7. State that knowing the exact diagnosis directs the treatment approach.

8. State that both diseases have very good treatment protocols, and even many cats with lymphoma can survive many years after just a few months of treatment.
9. State that we have mounting evidence that cats with IBD may transition to lymphoma as some people with Crohn’s Disease later develop lymphoma. Failure to act increases the likelihood that this will occur. Also state that many cats with IBD will go years before this transition. If you do not state this, the owner may jump to the conclusion that an older cat has lymphoma and request treatment without biopsies or even euthanasia.

10. State that the lymphoma protocol using lomustine has minimal, if any, side effects. Many owners know the side effects of chemotherapy and will reject chemotherapy prematurely. State that the treatment is given only every four weeks and given orally and that the cat is not hospitalized for the treatments.

11. Avoid using three terms too often or prematurely. A) Chemotherapy. Rather, refer to having a “drug” or a “treatment” for lymphoma. After getting across the positives (lack of side effects, only given monthly, an oral treatment, no hospitalization needed) should you use the C word, if at all. B) Surgery. The invasiveness of this can be scary. As much as possible, talk about “collecting tissues,” “doing biopsies of the organs,” a rapid recovery with the cat going home after surgery as if nothing happened. However, do not leave them the false impression this is not surgery or is non-invasive. C) Cancer. This word often denotes hopelessness or a very hard struggle associated with treatment. Instead of using this term, say lymphoma. To us, there is not difference, but to many clients there is a big difference. We do not want our clients to let negative thoughts stop communication.

12. As they begin to seriously consider surgery, state that cats handle this kind of surgery MUCH better than we would. Note that they appear virtually normal the day they are discharged from the hospital.

13. Reiterate that we will have a comprehensive treatment plan because we are biopsying the small bowel, liver, and pancreas.

14. Schedule the ultrasound study and surgery as soon as possible. If we do the exam and ultrasound study in the morning (before our surgery time) and the schedule permits, we tell the owner that we can do surgery TODAY. If we must delay it until tomorrow, we recommend admitting the cat to the hospital now so we will be ready to go tomorrow morning. Buyer’s remorse is a very powerful force. If the cat goes home and is to return for surgery, the chances of a No Show are significant.

15. Dr. Todd Tams says: “Offer Plan A and keep your mouth shut.” This is a powerful selling technique. After offering Plan A, the course of action will be determined by the one (you or the client) who speaks first. If you speak first and offer Plan B, the client will take that. If the client speaks first, Plan A will be accepted.

Objections to Surgery & Treating Without a Diagnosis

The most common objections to surgery are 1) the cat is not a good surgical candidate, 2) the owner has financial limitations, and 3) it is too invasive for the owner. One or more of these often lead to a request for treatment without biopsies. Usually the owner asks to treat for IBD to see what happens.

The problem with this approach is that putting a cat with lymphoma on a course of steroids will usually achieve response to both diseases, so you cannot use response to differentiate them. In addition, and more importantly, lymphoma cats will have a temporary response followed by drug resistance. Subsequently, these cats do not respond well to the chemotherapy drugs.

If the client refuses surgery or if the cat is really not a good surgical candidate, treatment should still be considered. Although no veterinarian really wants to do this, it has its place. A food trial with a hypoallergenic diet is a reasonable approach unless spending six to eight weeks could be detrimental to the cat. If the cat has lost significant weight, this may not be a good approach. If a food trial is not performed or fails, medical treatment is still feasible with informed consent. My preference is to treat for lymphoma knowing that cats with IBD will respond to that approach. However, the problem comes in knowing when to stop treatment. I strongly prefer to stop after eight doses of lomustine, and I do not continue using steroids after that. If the cat has IBD, the clinical signs will return when treatment is discontinued. One could argue that if that occurs, putting the cat on steroids would be appropriate, and I would agree with that in most cases. It should control IBD, and it would not be harmful to the cat with lymphoma.