Introduction

This lecture will discuss developing concepts in controlling chronic renal disease in cats. Emphasis will be on the use of benazepril, an ACE-inhibitor, to control intraglomerular hypertension, calcitriol to prevent renal secondary hyperthyroidism, and high protein diets to prevent or reverse muscle wasting. Time permitting, other treatments will be touched upon including phosphate binders, potassium supplements, subcutaneous fluids, and darbepoetin and drugs to control systemic hypertension.

1) Benazepril
   a) Amer J Veter Research, 3/01: Shown to slow progressive deterioration of the kidneys in cats.
   b) Actions (per Novartis)
      i) Inhibits the Renin-Angiotensin-Aldosterone System
      ii) Vasodilation of the glomerular efferent arteriole
      iii) Reduces intraglomerular pressure (relieves glomerular hypertension)
      iv) Decreases protein loss
      v) Increases glomerular filtration leading to increased clearance of creatinine and urea.
   c) Dose: Up to 5 kg: 2.5 mg/q24h; Over 5 kg: 5 mg/q24h
      i) Most cats will take crushed tablets in canned food
   d) Potential side effects
      i) Azotemia or worsening of azotemia: happens initially in 30% of cats (and humans) but then the azotemia diminishes for several weeks to months.

2) Calcitriol
   a) Effects of calcitriol:
      i) The active form of vitamin D (25[OH]2); Made ONLY in the kidneys.
      ii) It has effects on at least 30 tissue sites in the body that bear its receptor, including the kidney and the parathyroid gland.
      iii) It controls synthesis of over 2000 proteins: it increases 50 and decreases 40 in the kidneys alone.
      iv) Induces formation of specific calcium receptors in the kidneys with their critical regulation of calciuria causing Ca resorption in the renal tubules.
      v) Increases calcium mobilization from bones if the above two mechanisms are not sufficient.
   b) Effects relative to renal disease
      i) Increases Ca in the blood.
         (1) Increases Ca resorption in the kidneys.
         (2) (Increases Ca mobilization from the bones.)
   c) Renal disease leads to phosphorus retention
      i) The kidneys are not able to excrete it properly.
      ii) Hyperphosphatemia causes appetite depression.
      iii) Three Possible Solutions
         (1) Lower blood level of P (Plan A)
            (a) Proper renal excretion of excess P
            (b) Cannot happen in kidney disease
         (2) Raise blood level Ca
            (a) Increase calcitriol production by the kidneys because it (Plan B)
               (i) Decreases renal excretion
               (ii) Mobilizes from the bones
               (iii) Cannot happen because calcitriol production stops in renal disease.
            (b) Stimulate the parathyroid glands (Plan C)
               (i) Increased PTH is produced in the parathyroid glands.
               (ii) Parathyroid function increases by hyperplasia (increased number of cells) and hypertrophy (increased size of the cells) of the parathyroid cells.
Ca increases due to mobilization of Ca from the bones, increased GI calcium uptake, and decreased urinary calcium loss (same results of calcitriol).

Results in Renal Secondary Hyperparathyroidism (RSHPT).

Calcium increases in the blood. Ca:P ratio normalizes.

Problem solved, except …

1. Once hypertrophied, the parathyroid glands cannot be slowed or stopped.
2. Calcium increase becomes excessive.
3. Calcification occurs in tissues, notably the kidneys.
4. Rapid deterioration of kidney function follows.
5. The cat is in renal failure; death ensues.

d) Once parathyroid hyperplasia begins, the body has no way to down regulate the parathyroid gland; this leads to RSHPT.

Our Goal

i) Do not let RSHPT get started.
(1) Because we cannot stop it.

ii) To do so:
(1) Replace calcitriol before the cascade begins.
(2) Begin as early as possible because renal production of calcitriol stops when the creatinine becomes abnormal.
  (a) Begin before phosphorus elevates.
  (b) Begin as soon as renal disease is detected.
(3) NOTE: 100% of cats with chronic renal disease of long enough duration will ultimately develop RSHPT according to Dr. Nagode.

RSHPT leads to

(a) Lethargy
(b) Decreased appetite
(c) Weight loss
(d) Further deterioration of nephrons
(e) Renal failure and death.

Response to calcitriol is seen as

(a) Increased appetite
(b) Weight gain
(c) More alert and active
(d) Increase in longevity.

e) The Proof: Nagode-Norsworthy-Chew Study

i) Three groups
(1) Gr. 1: Renal Diet Only
(2) Gr. 2: Renal Diet + Benazepril
(3) Gr. 3: Renal Diet + Benazepril + Calcitriol

ii) Survival from diagnosis
(1) Gr. 1: 430 days (1.2 years)
(2) Gr. 2: 590 days
(3) Gr. 3: 1038 days (2.8 years)

iii) Creatinine increase during the first year.
(1) Gr. 1: 2.3 mg/dl
(2) Gr. 2: 1.3 mg/dl
(3) Gr. 3: 0.4 mg/dl

iv) Slower weight loss per year
(1) Gr. 1: 9.5% WL per year.
(2) Gr. 3: 4.9% WL per year.

f) Twice per week dosing is required when …

i) Phosphorus is > 6.0 mg/dl but < 7.0 mg/dl
(1) Feed low P diet (low protein or geriatric)
(2) Give a non-calcium containing phosphate binder
  (i) Phosphate binders
    1. Good: aluminum hydroxide
      a. General Dose: 50 mg BID in food. (Actual dose: To Effect)
      b. Conseal-AIH; www.bockvetpharma.com; chewable tabs
      c. USP grade powder; www.letcomedical.com; 500 gm for $55 + shipping.
      d. Mix in canned food or “shake in a baggy” with dry food.
      e. Dose for 5 kg cat: Rounded ¼ teaspoon BID in food
f. Dose may be doubled to reduce serum phosphorus to < 5.0 mg/dl.
g. A 2 month’s supply fills a 26 dram prescription vial.
h. Phos-Bind, www.RXVitamins.com

2. Not good: calcium-containing
   a. Calcium acetate (PhosLo)
   b. Calcium carbonate (Epakitin)
   c. These will produce hypercalcemia ROUTINELY when using calcitriol.

(3) You are not able to perform iCa levels.
   a. In-house testing is preferable (iStat or equivalent) because it is reasonably inexpensive to perform and you get an answer in less than 10 minutes.

ii) Hypercalcemia
   (1) If iCa is elevated, verify with iCa: Michigan State U or i-Stat or equivalent
      a. iCa is abnormal if it is 0.1 over the high end of normal; N = 1.0-1.32 mmol/l.
      b. iCa underestimates increased iCa about 40% of the time.
      c. In-house testing: serum, whole blood, or plasma but no EDTA.
      d. Commercial lab: serum preferred but plasma (without EDTA) is OK.
   (2) Solution
      a. Alendronate (Fosamax): 10 (to 30) mg q7d

iii) If iCa is not performed.
   a. The safest approach is to only use 2X per week.

2.5 ng/kg q24h PO is recommended
   (1) This is the typical schedule to use when the serum calcium and phosphorus are in the normal range.
   OR

   (2) A twice weekly schedule
      a. Typically, 9 ng/kg every 3.5 days (2X per week)
      b. This can also be used if the serum calcium and phosphorus are in the normal range.

      (c) This is the schedule you must use when the serum calcium or phosphorus is elevated.
         i. Use it if you are not able to run ionized calcium levels.

   iii) US Compounding; 800-718-3588; Conway, AR.
      (1) Plan A: Nagode System using 0.25 ml per dose regardless of weight of the cat and daily vs. 2X/week dosing schedule. However, nine concentrations are made and sold directly to the client. See chart below.
      (2) Plan B: Norsworthy System using four concentrations that are purchased by the veterinarian in 1, 4, or 8 oz. quantities and dispensed by the veterinary practice to clients. The dose (quantity) is NOT standardized as in Plan A. See chart below.

   iv) Caution: A twice per week prescription and a daily prescription are different concentrations. Be sure your clients know not to use them interchangeably. Only use it as stated on the prescription label.

2. How to Begin
   i) Understand how CTA works and how it is beneficial to the cat.
      (1) All veterinarians in the practice
      (2) Remainder of your staff: receptionists and technicians.

   ii) Decide if you are going to prescribe it or dispense it.
(1) Ask your pharmacist if your state permits this.

iii) Decide when you plan to begin treatment.

(1) 40% Loss: Cr=1.6+; SDMA=15+
(2) 75% Loss: Creatinine=2.2+ (2.5+) (above normal reference range for your machine/lab)

iv) If you are going to dispense it:

(1) Order calcitriol and supplies
   (a) Calcitriol: which pharmacy to use? US Compounding; 800-718-3588; Conway, AR
   (b) Order unflavored; much better acceptance than chicken or fish
   (c) Dark, glass bottles; calcitriol reacts with prolonged contact with plastic
   (d) OK to dose with plastic syringes, but the amber dosing syringes are preferred because the lettering on the side of the syringe is not dissolved by calcitriol.

(2) Tell client not to refrigerate or freeze calcitriol; it is ineffective when it warms up.

k) Develop your presentation to clients
   i) Your cat has lost XX% of renal function.
   ii) Kidneys are like new cars.
      (1) New cars are used cars as soon as they leave the dealership.
      (2) Kidneys begin wearing out during the first year of life.
      (3) Show graph with known loss points.

Plan A: Calcitriol Dosing Dispensed by Pharmacy

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Daily Schedule</th>
<th>Twice Per Week Schedule**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 ng/kg q24h PO</td>
<td>9 ng/kg q3-4d PO</td>
</tr>
<tr>
<td>0-5 pounds</td>
<td>4 nanograms</td>
<td>16 nanograms</td>
</tr>
<tr>
<td>5-7 pounds</td>
<td>8 nanograms</td>
<td>24 nanograms</td>
</tr>
<tr>
<td>7-10 pounds</td>
<td>12 nanograms</td>
<td>32 nanograms</td>
</tr>
<tr>
<td>10-14 pounds</td>
<td>16 nanograms</td>
<td>48 nanograms</td>
</tr>
<tr>
<td>14-21 pounds</td>
<td>24 nanograms</td>
<td>80 nanograms</td>
</tr>
<tr>
<td>21-29 pounds</td>
<td>32 nanograms</td>
<td>96 nanograms</td>
</tr>
</tbody>
</table>

Note: Dose for all body sizes whether daily or twice per week: 0.25 ml. The calcitriol amounts above are in 0.25 ml of liquid.

** Must be used when Ca or P is elevated.

CAUTION: A twice per week prescription and a daily prescription are different concentrations (so the actual administered amount is 0.25 ml). Do not use them interchangeably. Only use it as stated on the prescription label.

Plan B: Calcitriol Dosing Dispensed by the Veterinary Practice*

<table>
<thead>
<tr>
<th>Weight (#)</th>
<th>Daily Schedule</th>
<th>Twice Per Week Schedule**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/ml</td>
<td>ml/day</td>
</tr>
<tr>
<td>up to 7.0</td>
<td>26</td>
<td>0.25</td>
</tr>
<tr>
<td>7.0-9.9</td>
<td>26</td>
<td>0.40</td>
</tr>
<tr>
<td>10.0-12.9</td>
<td>26</td>
<td>0.50</td>
</tr>
<tr>
<td>13.0-17.9</td>
<td>72</td>
<td>0.25</td>
</tr>
<tr>
<td>18.0+</td>
<td>72</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*This is legal in many states & varies by pharmacy. Check with your pharmacist regarding your state.

** Must be used when Ca or P is elevated. Otherwise, either dosing schedule is effective.

CAUTION: A twice per week prescription and a daily prescription are different concentrations. Do not use them interchangeably. Giving the higher (2X/w) concentration daily will result in hypercalcemia and calcification of the kidneys. Only dose as stated on the prescription label.
My approach

Creatinine = 1.6-2.1: Calcitriol
Creatinine = 2.2-4.0: Calcitriol + Benazepril + Renal Diet
Creatinine = 4.0+: Add SC fluids

Thanks to Larry A. Nagode, DVM, PhD, Ohio State University, for information and inspiration.
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

![Graph showing progression of kidney disease with creatinine levels and function percentages.]

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 produced exclusively in the kidneys until kidney 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 vitamin D made by the kidneys, it has no side-effects as long as it is dosed properly.
3) Renal diet
   a) Traditional Renal Diets
      i) Reduced protein (controversial)
      ii) Reduced phosphorus
      iii) Non-acidifying
      iv) Low sodium
   b) New thinking; Credit to Deb Zoran, DVM, PhD (Nutrition), DACVIM
      ii) Older cats have reduced ability to digest protein.
      iii) Older cats have an increased maintenance energy requirement (MER) in contrast to older dogs.
      iv) Older cats have an increased need for protein instead of a decreased need as in dogs.
      v) Therefore, feeding a low protein diet to an old cat can result in severe protein deprivation leading to muscle wasting.
      vi) Cats need far less carbohydrate than we have fed in the past.
      vii) Many feel we should be feeding high protein diets to older cats, even ones in renal insufficiency.
         1) Change to a traditional renal diet if the BUN increases significantly realizing that the BUN will definitely go up disproportionally to creatinine.
         2) High protein diets may increase the need for phosphate buffers (high protein diets are high in phosphorus), the need to monitor blood pressure more closely (renal diets are low in sodium), the need for potassium supplementation (renal diets are supplemented with extra potassium), and alkalization of urine (high protein diets are strongly acidifying). Monitoring should include creatinine, BUN, phosphorus, potassium, TCO2 or HCO3, and blood pressure determination.
         3) High protein diets are contraindicated in cats with a history of calcium oxalate urolithiasis because they are so strongly acidifying.
      viii) See handout for clients at end of this handout.
   x) Journal Feline Medicine and Surgery, August 2013
      1) “Animals, including cats, can adapt to low protein intake and maintain nitrogen balance while depleting LBM (lean body mass). 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 5.2 g/kg body weight, well in excess of current AAFCO and NRC requirements.”

4) Drugs to increase food intake
   a) Famotidine; corrects gastric hyperacidity
   b) Cyproheptadine
   c) Mirtazapine: 15 mg tablet: 1/8 tablet (~2 mg) q48h (q24h if renal function normal)
      i) Has marked GI and cardiac stimulant effects if overdosed (definitely at 15 mg/dose)
      ii) Better to have it compounded into a 2 mg tablet.
   d) FortiFlora (Purina): sold for diarrhea control but some cats eat much better with it in their food.
   e) Benazepril (main “side effect” is appetite stimulation and weight gain).
   f) Vitamin B12 injections: 250-2000 mg q3-14d.

5) Pilling Cats: https://dl.dropboxusercontent.com/u/69563616/Pilling%20Demo.AVI

6) Rechecks
   i) Review of the visit when the diagnosis is made
      1) Chemistry profile + CBC (PCV) +/- UA
      2) If creatinine is 1.6 or greater: add ionized calcium
      3) If creatinine is 1.6-2.1: dispense calcitriol
      4) If creatinine is > 2.1: dispense calcitriol + benazepril + renal diet
         a) PRN: K supplement; P binder, SC fluids, appetite stimulant.
   ii) Most vital tests: creatinine, BUN (esp. very thin cats), phosphorus, tCa/iCa, potassium, PCV, (TCO2 or HCO3), blood pressure.
   iii) First should be about 4 weeks after treatment begins.
      1) To check compliance
      2) To check creatinine/BUN, potassium, phosphorus, iCa.
      3) Check iCa before calcitriol is started and at the first recheck after it calcitriol is started.
      4) Check blood pressure – do this first and with the owner present.
   iv) Every 3 months thereafter.
      1) Review medications and diet.
(2) Check the cat’s weight.
(3) Same tests except
   (a) iCa every 6-12 months if the dose of calcitriol is consistent and the tCa is stable.
   (b) Blood pressure every 6-12 months if the creatinine has not changed significantly.

v) I perform my rechecks in-house using the VetScan by Abaxis (The “Cat Friendly” Machine)
   (1) Takes less than 15 minutes of run time to get results.
   (2) Runs on whole blood.
   (3) I go to another exam while it is running.
   (4) This approach allows changes in the treatment protocol without having the client return.
   (5) No phone call is needed the next day when you have forgotten the details of the case or when you have to leave a message.

The Life and Times of old cats are getting ... Better and Longer.

It’s a great time to be an old cat, to own an old cat, and to treat old cats.