13th Annual Fred Scott Feline Symposium

July 27-29, 2001

College of Veterinary Medicine
Cornell University
Ithaca New York

13th Annual Fred Scott Feline Symposium

Friday, July 27, 2001

7:00 am	Registration
8:30 am	Fungal and Viral Skin Diseases – W. Miller
10:00 am	Break
10:30 am	Disorders Causing Hair Loss, Exfoliation, or Both – W. Miller
12:00 noon	Lunch
1:00 pm	The "Bread and Butter" of Practice: Itchy Skin Diseases – W. Miller
3:00 pm	Break
3:30 pm	A Lump, A Bump, and Leftovers – W. Miller
5:00 pm	Free Time
6:30 pm	Picnic – Stewart Park

Saturday, July 28, 2001

8:30 am	Diabetic Ketoacidosis – N. Dhupa
10:00 am	Break
10:30 am	Transfusion Medicine – N. Dhupa
12:00 pm	Lunch
1:00 pm	Feline Hyperthyroidism: 6000 Cats and Counting – J. Turrel
3:00 pm	Break
3:15 pm	Management of Vaccination Induced Sarcomas – J. Turrel
4:00 pm	Feline Skin Tumors – J. Turrel
5:00 pm	Adjourn

Sunday, July 29, 2001

8:30 am	Idiopathic/Interstial Cystitis – D. Chew
10:00 am	Break
10:30 am	Urethral Obstructions and Urolithiasis - D. Chew
12:00 pm	Lunch
1:00 pm	Chronic Renal Failure and Treatment - D. Chew
3:00 pm	Break
3:30 pm	Systemic Hypertension, Hyperthyroidism and the Kidney, Renal Transplantation - D. Chew
5:00 pm	Adjourn. Have a Safe Trip Home!

Teaching Faculty

William H. Miller, Jr., V.M.D., Diplomate, A.C.V.D., Professor of Dermatology, Medical Director, Cornell University Hospital for Animals

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Jane M. Turrel, D.V.M., M.S., Diplomate, A.C.V.R., A.C.V.I.M. (Oncology), A.C.V.R. (Radiation Oncology), Owner/Practitioner, Veterinary Oncology Specialties, 225 Carmel Ave., Pacifica CA 94044

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CHEMOTHERAPY CLINICAL TRIAL FOR CATS WITH SARCOMAS

The incidence of soft tissue sarcomas in cats has risen significantly during the last decade. There is epidemiological evidence that vaccines are associated with this increase. The combination of surgery and radiation therapy provides the best control for these tumors in cats. However, many cats still fail to be cured. Chemotherapy is indicated for cats with soft tissue sarcomas when surgery or radiation therapy is not possible or has not been successful. The combination of chemotherapy and radiation therapy may also help to control sarcomas in cats.

Ifosfamide is one of three chemotherapeutic agents that have proven significant activity against soft tissue sarcomas in people. Response rates have been superior to those seen with doxorubicin. We recently evaluated ifosfamide in tumor bearing dogs and measurable responses were observed. *The purpose of the present study is to document evidence of antitumor activity when ifosfamide is used to treat cats with vaccine-associated sarcomas*. If ifosfamide proves effective, we anticipate incorporating its use in combination with radiation therapy and surgery.

Eligibility criteria:

- Biopsy-proven soft tissue sarcoma
- Measurable disease must be present
- No prior chemotherapy, radiation therapy or surgery
- No cardiac, renal or hepatic disease

Cats will be seen by an oncologist for an initial appointment and evaluation and then treatment with ifosfamide will be scheduled. Ifosfamide is given with saline diuresis over 6 hours. Bloodwork will need to be obtained days 7, 14 and 21 after treatment. If cats respond to ifosfamide, treatments will be continued every 21 days. If there is no response, the owners may explore other treatment options.

***Funding is available for this chemotherapy trial.** If you have questions about the *ifosfamide study* or have a client interested in participating, please contact the oncologists at Cornell at (607) 253-3060.

* Funding provided by the Vaccine Associated Feline Sarcoma Task Force and Winn Feline Foundation

Fungal and Viral Skin Disorders of the Cat

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Viral Disorders

FeLV/FIV

The feline leukemia and immunodeficiency viruses usually affect the skin via their immunosuppressive actions, e.g., recurrent abscesses, general unthriftiness, etc. Because these viruses persists in the cat's body, the cat may develop an immune complex disorder which can present as skin disease, polyarthropathy, or a lupus-like condition. Some "specific" disorders associated with these viruses are:

FeLV Cutaneous Horns: Multiple cutaneous horns that develop in a mature cat need investigation since something is triggering the focal epidermal proliferation. In addition to FeLV, squamous cell carcinoma (spontaneous or viral induced) or other epithelial tumor types must be considered.

FeLV Exfoliative Dermatitis: A pruritic, crusting dermatitis involving the head/neck and elsewhere of the mature cat Response of the condition to steroids, antibiotics, etc is poor and the cat feels poorly. On skin biopsy, there are syncytial-type giant cells in the epidermis and outer root sheath of the hair follicle. Apoptotic cells are common, especially around the giant cells.

FIV Demodicosis: Demodicosis caused by *Demodex cati* is rare in the cat and all(?) cases of recurrent/recalcitrant disease have some underlying immunosuppressive disorder. Demodicosis caused by *Demodex gatoi* is <u>not</u> associated with immunosuppression.

FIV Exfoliative Dermatitis: A rare dermatitis characterized by a generalized, nonpruritic papulocrustus eruption most pronounced on the head and limbs. The basal cells of the epidermis show a pallor not seen in other feline disorders.

Feline Cowpox Virus Infection

A European condition primarily but an occasional case has been recognized in the US. Cats become infected while hunting infected rodents. Peak incidence in the fall. Viremia with or without pyrexia, anorexia, etc follows the bite and then 10 to 14 days later more classical pox lesions appear. Self-cure is the rule. Zoonotic for cats, dogs, and humans.

Feline Infectious Peritonitis

Skin disease beyond that due to decreased grooming is extraordinarily rare in this disease. Because the virus persists, and immune complex/vasculitis presentation can be seen.

Feline Rhinotracheitis Infection

The true incidence of skin lesions associated with this α-herpesvirus is unknown but probably is very low. A pre-existing immunosuppression may be needed for significant lesions to occur.

An ulcerative and necrotizing facial dermatitis and stomatitis has been associates with herpes infection in adult cats with or without the history of more classical respiratory signs. An occasional kitten may also develop the dermatitis. Affected cats develop an ulcerative, crusted dermatitis of their face primarily. Skin biopsies are necessary to separate this condition from drug reaction, pemphigus, or other ulcerative conditions. Here, the surface and follicular epithelium contains multinucleated keratinocytes which may contain inclusion bodies. Treatment with lysine (250 mg q24h) and/or α-interferon (60-120 IU/cat/day) may have some benefit.

Feline Papillomavirus Infection

Papillomavirus infection in the cat is relative new. Although there are reports of cats with singular lesions, most focus on multicentic disease with a sharply-demarcated dysplastic skin condition. These lesions are typical of those seen in humans with Bowen's disease. The original dysplastic lesion gradually become frankly neoplastic (squamous cell carcinoma *in-situ)*. In humans, tumor cells which breach the epidermis tend to metastasize quickly. That does not appear to be the case in cats. Lesional treatment with laser surgery (viable viral particles in vapor!!), pliseotherapy, etc does not prevent the development of new lesions.

Fungal Disorders

Dermatophytosis

Ringworm is alive and well in the cat population and, until an effective vaccine is available, it will be the bane of every cattery owner. The only real changes in this disease are the advances made in treatment.

Although clipping will result in more clinical lesions, the removal of infected hairs is very important for long term control. Cats should be treated with local agents and wholebody agents since they often has unrecognized areas of active disease.

Cattery Recommendations:

1. Suspend all travel in and out and culture all cats
2. Separate infected, non-infected, and uncertain status (culture pending) cats.
3. Topical and systemic treatment of all nonpregnant adults and kittens over 12 weeks of age.
    a. Griseofulvin:

Microsized: 25-60 mg/kg q12h Ultramicrosized: 2.5-15mg/kg q12h

b. Ketoconazole: 5-10 mg/kg q24h
c. Itraconazole: 5 -10 mg/kg q24h
d. Fluconazole: 50 mg/cat q24h
e. Terbinafine: 20 mg/kg q48h

4. Culture "cured" individuals 3 times at weekly intervals. Remove to uncertain room while results are pending.
5. Burn down the cattery!

Malassezia Dermatitis

Malassezia pachydermatis is a lipophilic, non-lipid-dependent, nonmycelial saprophytic yeast that is a normal inhabitant of normal dogs and cats. Six other lipid-dependent species (*M. furfur, M. globus, M. obtuse, M. restricta, M. slooffiae, and M. sympodialis)* can also be found. Normally, very small numbers of these organisms are found in the ear canals, middle ear, oral cavity, skin (especially intertrigenous regions), anal sacs, and vaginal, prepucial, and anal mucosa. Moisture encourages replication and increases the normal population of yeast on the body.

Malassezia dermatitis is common in dogs and rare (or rarely recognized?) in the cat. Yeast proliferate in response to some insult, e.g., hypersensitivity, swimming, etc. Once the yeast reach some critical mass, the underlying disorder can be removed but the yeast and the symptoms they produce will persist until specifically treated. Beyond allergy, be it atopy or food hypersensitivity, the trigger event in cats is uncertain.

Clinical Signs

In the nonpruritic animal there is the surface accumulation of scale (cat), scale-crust (dog, cat), or wax (dog). In the dog, significant numbers of yeast produce a characteristic smell. In the ear canals, toe webs, face folds, axillary areas, and other intertrigenous zones, inflammation and pruritus are usually present. As can be seen, the trouble spots for *Malassezia* are the classic areas of pruritus in allergy. In well over 50% of the chronic allergic dogs examined by the author, the atopy or food hypersensitivity is complicated by a secondary *Malassezia* dermatitis. The same phenomenon occurs in the allergic cat but the frequency is much lower.

Diagnosis

Although Malassezia dermatitis or otitis can be suspected by the smell of the animal's skin or ears or by the nature of the surface changes, the diagnosis needs to be confirmed by cytologic demonstration of "excessive" numbers of organisms or by histopathology. Cytology is least expensive and most rapid and is the preferred method of diagnosis. For truncal lesions, surface debris is collected by pressing a clean glass slide, clear cellophane tape, or specially manufactured gel-coated slide to the involved area. The area can also be scraped with a scalpel blade. Around the face and toes, material is best collected with a dull scoop or a Q-tip. The author uses the blade and Q-tip techniques. Sample material is transferred to a slide and stained with either Diff-Quik or New Methylene Blue. Diff-Quik is difficult to use with cellophane tape or gel-coated

slides. Since the first fixative of Diff-Quik is alcohol based, the slide should be briefly heat fixed before staining.

Various authors have defined the number of yeast they consider normal, e.g., ≤1/HPF, and figures vary with collection technique and magnification used (40X, 100X). Humidity and sample site enter the picture as well. For example, more organisms will be found in the inguinal region during the moist summer months and folded areas, e.g., claw fold, always have more organisms then the surrounding skin on the digit. Another often forgotten variable is whether the animal is licking or scratching the area. Mechanical trauma removes surface debris and yeast. Traumatized areas should be avoided during sample collection. With all these variables, the author believes it is very difficult to define what a normal number of yeast is and slide interpretation must always be considered in light of the patient before you. In most cases, the diagnosis of yeast or not will be straight forward - yeast will abound or none will be seen. With practice, yeast can be seen with the 10X objective. At 40X, they jump out at you and the author believes that oil emersion never is needed. If the animal looks and smells like yeast should be present but none are seen make sure the specimen is examined carefully (40X) for Staphylococcal overgrowth. In some cases (Staphylococcal hypersensitivity?), what appears to be due to yeast is due to bacteria.

In the odd case, the cytologic finds don't fit the clinical picture and more samples should be evaluated to resolve the dilemma. Skin biopsy can be useful in these troublesome cases. When biopsy is to be used, the hair in the area should not be clipped closely (leave at least ⅛ inch long) and no surface cleaning can be done. Areas where the animal is known to lick or scratch should be avoided if possible. If these areas can not be avoided, biopsy the areas at edge where the surface epithelium stands the most chance of being intact.

Treatment

The first rule of treatment is to determine why the *Malassezia* dermatitis is present. Is the animal allergic? Does it have a primary or secondary seborrheic condition? Is its cutaneous ecology being affected by antibiotics or steroids? The list goes on. If the yeast are addressed but the underlying cause is ignored, the infection will recur or will not respond as rapidly or completely. Conversely, resolution of the underlying disease may result in the spontaneous disappearance of the yeast.

Since *Malassezia* in a noninvasive organism, topical treatments can be sufficient to resolve the dermatitis provided that the animal isn't hypersensitive to the yeast. With hypersensitivity, the hidden organisms (anal sacs, middle ear, vagina, etc) may liberate enough antigen that the allergic reaction will continue despite the diligent use of appropriate topicals. Is that residual foot licking because the cat is atopic and needs allergy testing or is it a sign of a *Malassezia* hypersensitivity? Since *Malassezia* antigen is not available commercially for skin testing, clinical impression is critical in these cases. Is the pruritus steroid non-responsive? Is the itching intense but the number of yeast low? Has the cat had repeated bouts of *Malassezia* dermatitis? If the hypersensitivity is proven or strongly suspected, systemic treatments will be needed.

Systemic treatments to be used include ketoconazole (10 mg/kg q24h), itraconazole (5 mg/kg q24h), or fluconazole (10-20 mg/kg q12-24h). Itraconazole and fluconazole are safer then ketoconazole but much more expensive. Ketoconazole is now available in generic formulation which has significantly reduced its cost ($1.30/200 mg tab @CUHA). Typically, a 30 to 45 days course of treatment is needed if topical treatments aren't used. Topicals can shorten the course of systemic treatment but no set figure on how much shorter can be given. The rule of thumb used to determine when to stop treatment in bacterial disease (7 to 14 days beyond clinical cure) is appropriate for *Malassezia* as well.

If the cat doesn't turn into a killer with topical treatments, shampoos can be valuable as either an adjunctive or the sole treatment of *Malassezia* dermatitis since the bathing mechanically removes the yeast, the active ingredients in the shampoo can actually kill some of the organisms, and the surface ecology of the skin is significantly altered, disfavoring yeast growth. The shortcoming of bathing is that not all areas are cleaned as well as others and the active ingredient is removed when the suds are rinsed. With no residual product on the skin, the cat can reinocuate the skin from its oral or anal population. Residual products are very limited in the United States and include Resichlor Rinse with Spherulites (Virbac), LymDyp (DVM), or a 50:50 solution of vinegar and water (Wegmans). The efficacy of the Resichlor rinse is unproven at this time. In Canada, enilconazole (Imaverol) is available as a dip and is very effective. Clients can have this product mailed to them by a Canadian veterinarian provided that they have a valid client relationship with the veterinarian.

For local disease, e.g., face folds, or ears, topicals with antifungals (Panalog, Otomax, Baytril Otic, Tresaderm, etc) all work well. Remember that wax can protect the yeast from the active ingredient and regular cleaning is needed.

Candidal Dermatitis

Candida spp. yeasts are normal inhabitants of the alimentary, upper respiratory, ear canal, and genital mucosa of probably all mammals. Candidiasis is a very rare disease in domestic animals. Proliferation requires alteration in the cutaneous or mucosal ecology or immunosuppression. In women, vaginal candidiasis is a common sequella to antibiotic treatment. In dogs and cats, antibiotic use in the immunologically normal animal does not predispose to candidiasis. In most cases, the candidiasis is associated with local alteration of the cutaneous environment in an immunosuppressed patient. Immunosuppression or altered ecology by itself appears to be insufficient to cause infection.

Since *Candida spp.* yeasts form hyphae they invade the epithelium, resulting in an ulcerative dermatitis. Unlike Malassezia which produces a fairly classical odor and clinical picture, *Candida* does not. The only way to determine whether the ulcerative lesions seen are due to *Candida,* toxic epidermal necrolysis, pemphigus, or any of the other differential diagnoses is to demonstrate the yeast by cytology or histology. In contrast to Malassezia, Candida show narrow-based and multilateral budding and pseudo hyphae or true hyphae can be present.

In candidiasis, both systemic (ketoconazole or itraconazole) and topical treatments are needed Moisture needs to avoided and topicals containing steroids are contraindicated in most cases.

Disorders Causing Exfoliation and Hair Loss

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Exfoliative Disorders

Exfoliative disorders are those where the stratum corneum is shed in large sheets rather then as individual and therefore invisible cells. Disorders of keratinization, although not strictly an exfoliative disorder, are considered here.

I. Primary Keratinization Disorders

Unlike the dog where primary seborrhea is fairly common, it is rare in the cat.

Generalized Disease: Recognized most commonly in Persians. Signs at or near birth. Variable expression so some kittens are worse then others. Greasy, unmanageable coat with ceruminous otitis and multiple comedones. Diagnosis by history and biopsy. Treatment by bathing? Retinoids unproven.

Localized Disease:

Feline Acne: Common problem. Can be a one-time disorder, a chronically relapsing condition, or a permanent problem. Comedones around the limps and on the chin. Simple cases require no treatment or respond nicely to topical treatment. Resistant cases should be examined carefully for secondary bacterial or *Malassezia* infection. Fatty acid supplement (DermCaps) can be of some benefit in chronic cases. Retinoids have worked but very few cases reported.

Stud Tail: An uncommon problem seen most commonly in intact males but can be seen in neutered males and altered and unaltered females. Accumulation of keratosebaceous debris along the entire dorsal surface of the tail. Castration does not resolve the problem but may slow its progression. Frequent cleaning with a degreasing shampoo (e.g., SulfOxyDex) keeps condition under control.

Idiopathic Facial Dermatitis of Persian and Himalayan Cats: Seen primarily in young cats (<12 month of age). Nonpruritic initially but pruritus develops with time. Often secondarily infected with bacteria or *Malassezia.* No uniformly effective treatment reported.

II. Secondary Keratinization Disorders

a.Endocrine Causes

Hypothyroidism

Diabetes mellitus

Cushing's Disease (see hyperfragility syndrome)

b.Infectious Causes

Dermatophytosis: Generalized disease is uncommon except in longhaired kittens. When generalized disease is recognized, especially in an adult cat, a search for some underlying disease should be undertaken.

Malassezia infection: Rare?

c.Parasitic Causes

Demodicosis: Seborrheic demodicosis can be caused by *Demodex felis* or *Demodex gatoi.* Demodicosis caused by *D. felis* indicates that the cat has some serious underlying disease, e.g., FIV infection. The "virulence" of the triggering disease will influence the success of treatment. In mildly immunosuppressed patients, topicals (Mitaban, LymDyp, Frontline Spray) can resolve the skin lesions. Data on relapse rates are unavailable. In seriously immunosuppressed cats, topicals tend to work poorly. Daily ivermectin (0.3 mg/kg) by mouth or injection rapidly reduces the mite count. Data on duration of therapy and relapse rates are unavailable.

Demodicosis caused by *Demodex gatoi*, a.k.a. *Demodex shortstubby*, is far more common in the southern parts of this country. This mite is contagious from rodent (the point source of infection?) to cat and from cat to cat. Symptoms vary from none to seborrhea to intense pruritus. Since the mite is very small (use you 10x objective on your microscope!!) and only invades the surface keratin layer, the cat removes it easily while licking. Never scrape an area the cat is licking as this will be artificially negative. In cats who are furmowing their entire body, positive scrapings may be impossible to obtain. An ivermectin-response test does <u>not</u> exclude this diagnosis. Failure to respond to topicals (Mitaban, LymDyp, Frontline spray?) Excludes the diagnosis. All contact cats need to be treated.

Cheyletiella: As fleas increased in incidence, Cheyletiella infestation decreased since the classical flea control products usually kill this mite. With the popularity of Program and Advantage, the incidence is increase again. The mite typical is found in highest numbers over the dorsum with variable pruritus. Diagnosis is difficult especially when the cat is itchy. Best way to demonstrate the mite is with the flea comb or vacuum cleaner. The mass of hair and scale that is collected is best evaluated by means of floatation techniques. These techniques are at best diagnostic 65% of the time. Ultimate test is response to treatment. Ivermectin (.3 mg/kg q14d for 2 to 4 treatments) receives widest use. Use of a topical agent at the first treatment can accelerate response in the very itchy cat.

Misc: Lice and fur mites cause scaly lesions but their size (lice) or numbers (fur mites) make diagnosis straight forward. Ectopic ear mites can cause disease on the body and are difficult to find in this location. However, these cats always have bad ears. Ectopic infestation best treated with

topicals or ivermectin.

d. Metabolic causes

Cats with liver or pancreatic disease usually with develop a generalized greasy coat. Since the greasiness tends to occur late in the course of the disease, the prognosis for these cats is guarded.

e. Environmental Causes

Low humidity will dry a cat's coat. This is especially true when the cat is a heavy groomer. With grooming, water is put on the hair and skin and will evaporate rapidly when the relative humidity is below 40%. If one cat in a multiple cat household is dryer then the others, it would be appropriate to determine if the cat has some underlying skin condition which has increased its grooming. If the flakiness is strictly due to low humidity, moisturizers will work but most cats fail to see the sense of humor in their prolonged use.

III. Exfoliative Dermatoses

True exfoliative dermatoses are very serious disorders and are indicative of serious internal disease.

a. FeLV/FIV Disease

b. Drug Eruption

At Cornell, approximately 2% of the cats we see in dermatology have a drug eruption. If blood dyscrasias etc are counted, the number of cats with drug reactions increases sharply. The reaction can be an irritant one where the skin in areas of contact becomes inflammed. The most important area where this occurs is in and around the ears. Cats' ears are much more sensitive then dogs' ears and yet we tend to treat them in a very similar fashion. When an otitis externa in the cat that was responding nicely to treatment starts to worse, drug eruption should be seriously considered.

After an initial period of sensitization, typically 7 to 14 days, a drug reaction can anytime during administration. The reaction can occur during the 1st, 3rd, or 15th administration. Once the reaction occurs however, it will reappear at every subsequent administration. When a drug reaction occurs in a cat taking multiple drugs, the last drug added is the most likely culprit.

There is no specific pattern of reaction seen with a particular drug and the reaction pattern can change every time the drug is administer to the same cat. Nonlesional pruritus as seen in atopy and food hypersensitivity is a **very rare** manifestation of drug hypersensitivity - everything else is fair game! Although the diagnosis of drug eruption can be supported by some specific histopathologic changes, there are many cases where the pathology of the drug eruption mimics that of a naturally occurring disease, e.g., pemphigus foliaceous. If the animal is suspected to have a drug reaction, the drug should be stopped and the eruption should stops its progression with in 14 days. Depending on the nature of the lesions, e.g., superficial pustular vs ulcerative, the skin may heal completely during this withdrawal period.

c. Thymoma

The exfoliative dermatitis seen with thymoma is a rare disease of the middle-aged to old cat. The exfoliation usually starts around the head and neck and pruritus is typically absent. Hair loss, especially of the feet, can accompany the exfoliation. With time, the whole body can be affected. Some cats, especially orange ones, lose hairshaft pigment and turn white. Beyond the skin lesions, the cats usually are heathy. Skin biopsies show a cell-poor hydropic interface

dermatitis. Although not unique to this disorder, this reaction pattern is rare in other conditions of the cat and should prompt the appropriate thoracic evaluation. Only surgery is curative.

d. Parapsoriasis

An extraordinarily rare exfoliative condition. Separated from other conditions by skin biopsy where lymphocytes lineup with the basal layer of the epidermis and hair follicle. Immunosuppressive steroid therapy is necessary to resolve lesions and keep them in remission.

e. Cutaneous lymphoma.

Far less commonly recognized in the cat then the dog. Typically very slowly progressive. Limited to no data on the "best" treatment.

Nontraumatic Hair Loss Disorders

The most common cause of regionalized or widespread nontraumatic hair loss is unrecognized excessive grooming. The cat is a furmower but only does so when the owner is out of sight. In order of decreasing frequency, the real causes of feline nontraumatic hair loss are:

a. Defluxion disorders

Stress, e.g., fever, parturition, drug administration, etc, interrupts hair growth. With "mild" stress, the hairs start to grow again in a day or so but are left with a "dimple" in the hair shaft. This weakens the hair shaft and in 7 to 10 days, the hair breaks off at or near the skin's surface giving the coat a disheveled look. This process is called **anagen** defluxion. With more pronounced stress, the hair cycle is interrupted and all the hairs are put into the resting (telogen) phase. When the animal's skin returns to normal, usually 30 to 45 days later, all the follicles switch to anagen and the telogen hairs are pushed out. The affected cat undergoes an excessive shed and may go bald. This process is called **telogen** defluxion. Both of these conditions are self-limiting and are diagnosed by trichography.

b. Hair Shaft defects.

Congenital or acquired hair shaft defects weaken the hair shaft so that it breaks more easily during grooming or other normal activities. The most common acquired hair shaft defect in the cat is dermatophytosis. Others include Trichorrhexis nodosa, trichoptilosis and color dilution alopecia. Diagnosis by trichography.

c. Acquired skin hyperfragility syndrome.

A very serious metabolic condition of the aged cat where the skin becomes very thin and fragile but not hyperextensible. The most common cause is hyperadrenocorticism but it can occur with primary or secondary hyperprogesteronemia, various liver disorders, or pancreatic adenocarcinoma. Because of the severe catabolic nature of these conditions, hair growth stops and hair loss can be recognized in frictional areas. In some cats, the coat is dull and dry but no hair loss is obvious.

d. Mural folliculitis

Mural folliculitis is a recently coined histologic term used to describe the presence of cells within the hair follicle wall. The type of cell seen dictates the types of clinical conditions to be considered. For example, a neutrophilic mural folliculitis is most indicative of bacterial disease

but can be seen with various autoimmune disorders. Lymphocytes can suggest dermatophytosis, drug reaction, early lymphoma, or an idiopathic condition.

e. Endocrine disorders

Unlike the dog who develops hair loss early in the course of its endocrine disease, the cat rarely does so.

The Itchy Cat

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Pruritus, the sensation which evokes the need to itch, is a complex process which can be mediated centrally, peripherally, or peripherally with significant central modification. For years, psychogenic pruritus was thought to be important in the cat. Today we know that the vast majority of itchy cats are perfectly sane- their skin tingles, tickles, burns, or whatever and they respond in the expected fashion by itching. The premature diagnosis of psychogenic pruritus does the cat and its owner a great disjustice.

For some unknown reason, cat skin appears to be programmed to itch. The cat has a much more rapid and profound eosinophilic response then does the dog. The major basic protein found in these cell can damp an allergic reaction by breaking down histamine but can also accelerate the reaction by damaging collagen and by causing mast cell degranulation. In normal cats, the number of mast cells around the superficial dermal blood vessels can be nearly double that found in the dog (20/hpf vs 12/hpf). The number in allergic cats usually is even greater. These findings can lead to allergic amplification where the pruritus is well out of proportion to the allergic stimulus. At the initial allergic event, some mast cells degranulate and attract eosinophils into the area. When the cat itches, some additional mast cells can degranulate via the pressure caused during licking or scratching and a vicious cycle starts. Because of this amplification system, itchy cats usually require a longer course of steroids then do dogs. Cats have fewer steroid receptors then do dogs so they require higher doses of drug to control the same level of pruritus. The attack dose of prednisolone for the cat is 2.2 mg/kg/day and most itchy cats will require 10 to 14 days of treatment before the fire is taken out of the skin.

ALLERGIC DISORDERS

Allergic disease are the most common reason for the cat to itch and they appear to be increasing in frequency. As in the dog, some cats have more then one allergic disorder, e.g., flea bite hypersensitivity and atopy, so the diagnostic evaluation must continue until the cat is itch free.

Unlike the dog, the allergic cat has no predictable pattern for its pruritus. The atopic cat can have miliary dermatitis, facial pruritus, anterior body pruritus, whole body pruritus, traumatic alopecia anywhere, eosinophilic plaques, or eosinophilic granulomas.

Flea Bite Hypersensitivity:

Worldwide, the most common allergic skin disease of the cat. Fairly easy to diagnose but more difficult to control. Products like Program and Advantage have made life easier but by no means have solved the problem. Purified flea saliva is in the pipeline so we may be able to address the hypersensitivity in a specific manner in the next few years.

Atopy:

By definition, atopy is a genetically influenced disorder where the animal becomes allergic to normally innocuous environmental antigens. Was uncommon in cats but appears to be increasing in frequency. Except in purebred cats where signs occur early in life, the standard DSH starts to itch typically between age 3 and 5. Over 85% of atopic cats itch during the warm weather. Unlike the atopic dog where progression to nonseasonal pruritus is commonplace, most atopic cats stay seasonal for long periods of time.

Clinical signs are very variable and their severity influences when the cat is presented for treatment. With intense scratching, the cat is presented shortly after the itching starts. Cats who just groom excessively many not get bad enough for weeks to months on end. With the variability of signs and timing to presentation, it can be difficult to offer the tentative diagnosis of atopy when the cat first starts to itch. Good records are necessary to document the seasonally recurrent nature of the cat's problem.

Diagnosis:

History: Variable specificity

Physical: Minimal specificity

Steroid response test: Very helpful in ruling out atopy. The uncomplicated atopic cat must stop itching when the appropriate dose (2.2 mg/kg/day) of prednisolone is given. A poor response indicates that the cat is not atopic. However, a positive response does not mean that the cat is atopic.

Differential exclusion: The best method to support the diagnosis of atopy.

Allergy testing: The most specific method to document atopy. The testing not only confirms the diagnosis but defines the allergens so immunotherapy can be formulated.

Serologic Tests: At this point, the currently available serologic tests have such poor sensitivity and specificity that they are of very questionable value.

Intradermal Testing: The gold standard

Treatment:

Cats are resistent to steroid side effects so these drugs are used with regularity in the atopic cat. For cats with a short allergy season, DepoMedrol injections (4-5 mg/kg) are used frequently. As long as the young healthy cat does not require more then 3 or 4 injections per year, the margin of safety of this treatment is wide. When more frequent injections are required or the cats is old, oral steroids are safer. The drug is given daily to heal the rash and then on an alternate day basis to keep things under control. Prednisone (2.2 mg/kg/day) and methylprednisone (1.8 mg/kg/day) are safest but some cats do not respond to these drugs. Dexamethasone (0.2 mg/kg/day) or triamcinolone (0.2 mg/kg/day) usually work in these prednisone resistent cats but are not as safe because of their longer duration of action. These latter two drugs should be used every 3rd day if possible.

When steroids are not an option, nonsteroidal drugs or immunotherapy vaccines may be beneficial.

ANTIHISTAMINES

Antihistamines can minimize the impact of histamine on the animal's pruritus. Since histamine is only one of many mediators of pruritus, these agents are not uniformly effective. However, in some patients, the results with antihistamines are as good as they are with corticosteroids. Antihistamines should be avoided or used with caution in pregnant animals or animals with glaucoma, seizure disorders, retentive disorders, heart disease, or know allergy to antihistamines. Antihistamine

overdose can kill animals. Since ketoconazole is known to alter the liver metabolism of antihistamines in humans, it would be prudent to avoid the use of ketoconazole and antihistamines in dogs and cats. If both agents need to be used simultaneously, the patient should be monitored carefully. Of the hundreds of antihistamines available, the following have proved to be effective in dogs or cats.

Drug	Dog Dosage	Cat Dosage
Diphenhydramine	2.2 mg/kg q8h	----------
Chlorpheniramine	0.22 mg/kg q8h	2-4 mg/cat q12h
Hydroxyzine	2.2 mg/kg q8h	----------
Clemastine	0.05-0.10 mg/kg q12h	0.68 mg/cat q12h
Amitriptyline	1-2 mg/kg q12h	5 mg/cat q24h
Cyproheptadine	----------	2 mg/cat q12h

FATTY ACID SUPPLEMENTS

The first report on the antipruritic effects of specially-formulated fatty acid supplements appeared in the veterinary literature in 1988. That report and others prompted intense study with these agents. We know that these special supplements can control pruritus in some animals but what is not know is what is the best formulation and the optimum dosage of said. Several studies have shown that dogs are very individualistic in their response to these supplements, suggesting that there is no one best supplement. If one supplement does not work, another with a different formulation should be tried. If a supplement is to be effective, results will be seen before 21 days of treatment.

Supplement	Dog Dosage	Cat Dosage
DermCaps	Per label	Per label
EfaVet	Per label	Per label
Eicosapentaenoic acid	40 mg/kg q24h	??
Gamma linolenic acid	>40 mg/kg q24h	>8 mg/kg q24h

DRUG COMBINATIONS

Because of the vast number of mediators of pruritus and the narrow focus of nonsteroidal agents, many drugs reduce but do not eliminate pruritus. Simultaneous administration of two or more drugs, each with a different target mediator, can improve the efficacy of each drug. The steroid-sparing effects of antihistamines and DermCaps have been proven as has been the additive benefit of administering DermCaps with an antihistamine. The author routinely dispenses DermCaps with antihistamines. If the combination proves to be effective, the antihistamine is discontinued to determine if the DermCaps, the antihistamine, or both are responsible for the patient's improvement.

IMMUNOSUPPRESSIVE TREATMENTS

Simplistically, allergy is an overactive immune response to an allergen. If the allergen can not be eliminated and the pruritus can not be controlled with immunotherapy, corticosteroids, or nonsteroidal agents, the patient is destroyed. For the extra-special patient and client, immunosuppressive treatment may be beneficial. Agents which can be effective are:

Dogs: Azathioprine: 2 mg/kg q24h, Cyclosporin 5 mg/kg q24h
Cats: Chlorambucil: 2-6 mg/m^2 BSA q24h

IMMUNOTHERAPY

Immunotherapy is the most specific form of treatment for atopy. Response is allergen

specific so an allergy test must be performed to formulate a specific vaccine. Response rate in cats is approximately 75%.

Food Hypersensitivity:

Food allergy can occur in any cat and can occur at any age. The kitten or geriatric patient appears to be equally susceptible. Signs are variable and are nonseasonal provided the cat eats the offending "food" year-round. Foods include foods, water, snacks, rodents, and anything else that enters the cat's mouth. Accordingly, simply changing the cat's cat food is of limited value in the diagnosis and treatment of food allergy. The cat's (and owner's!!) whole lifestyle needs to be modified to prevent accidental ingestion of the "food".

Young cats with a sudden onset of a steroid nonresponsive, intensely pruritic disease are prime candidates for a food allergy. However, a steroid responsive fur mower might have a food allergy. The only way to say yes or no to food allergy is to investigate it. Unfortunately, serologic and intradermal allergy tests are of little or no use in the diagnosis of food allergy. Dietary change is the only reliable test. Although there are various "hypoallergenic" cat foods which appear to be very good in a large number of cats, there are no 100% effective commercial foods and homecooking is still advised. If a response is to be seen, it will be noticeable in the first 30 days of the diet. Complete response may take 10 or more weeks.

Treatment involves avoiding the offending food. The author asks the owners to challenge their cat with individual "pure" foods so that the specific allergen can be identified. Once the allergen, occasionally the allergens, are identified, the owner will be able to find a commercial food which agrees with the cat. Rarely, homecooking must be continued and the diet must be balanced with fatty acids, taurine, and vitamins and minerals.

Insect and Arachnid Hypersensitivity:

House dust mites and fleas are well know problems for allergic cats. In dogs, skin test reactions to insects (ant, black fly, moth, etc) are commonplace and may be of significance to some "atopic" dogs. Information of the significance of most of these insects in cats is lacking but they can play an important role in allergic pruritus.

MOSQUITO BITE HYPERSENSITIVITY

A uncommon (?) lesionally pruritic disorder. Signs during warm weather. Reactions significantly worse at each subsequent exposure. Diagnosis by documenting a seasonal eosinophilic dermatitis which resolves spontaneously with mosquito control. Corticosteroids accelerate healing. Skin testing and immunotherapy may be beneficial.

PARASITIC HYPERSENSITIVITY

IgE is both the antiparasitic and antiallergen antibody and some animals become clinically allergic to their parasites. If serologic allergy tests for cats become useful, antiparasitic IgE probably will interfere with the kinetics of the routine allergy test. All atopic cats should be parasite free for 30 or more days before serologic tests are performed.

Intestinal Parasite Hypersensitivity:Rare. Pruritic skin disease associated with roundworm or hookworm infection. Worming history of all pruritic cats should be reviewed.

Mite Hypersensitivity:Common. The cat itches well out of proportion to the number of mites present. Hypersensitivity makes diagnosis more difficult as some/many

mites are killed. Pruritus can persist for several weeks after all the mites are killed.

Heartworm Hypersensitivity: Rare. As heartworm disease becomes more common in cats, this disorder will be seen.

Miscellaneous Hypersensitivities:

Contact Hypersensitivity:

Drug Hypersensitivity:

Bacterial Hypersensitivity:

Malassezia Hypersensitivity:

Hormonal Hypersensitivity:

LUMPS, BUMPS, AND LEFTOVERS

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EOSINOPHILIC GRANULOMA COMPLEX

This complex still continues to plague us. The three components (eosinophilic ulcer, eosinophilic plaque, eosinophilic granuloma with collagen degeneration) have well established clinical features but looks and exudative cytology can be deceiving. If treatment difficulties are occurring, a skin biopsy should be performed before radical and expensive treatments are undertaken.

Ulcer: The name is a misnomer as there are no eosinophils in the lesions. Most cases are idiopathic. Cases which respond poorly to treatment may be secondarily infected and antibiotics should be considered.

Plaque: The most common presentation. Lesion full of mast cells and eosinophils. Lesion probably develops after mast cell degranulation (immunologic or nonimmunologic). Recurrent cases should be evaluated for allergies.

Granuloma: Occur in the mouth, on the chin, or on the legs. Most cases are nonpruritic and may reflect some transient or permanent primary collagen damage. In pruritic cases, eosinophils probably enter the area first and recurrent cases should be evaluated for allergies.

All forms and cases need to be treated until the lesion disappears entirely. Most lesions heal on the surface well before the dermal inflammation is gone and cessation of therapy at surface healing usually guarantees a relapse. Steroids are the first line of defense but antihistamines, DermCaps, and other agents used in allergic cats have some use. Lesions of the complex that were steroid responsive but have become steroid resistant are infected or have undergone metaplasia to a squamous cell carcinoma.

PANNICULITIS

Panniculitis is inflammation of the subcutaneous fat. In most cases, the fat becomes necrotic and the material discharges through the skin. The diagnosis of panniculitis is easy. The determination of its underlying cause is difficult and successful treatment requires that the cause be determined.

Post-vaccinal: Solitary lesions of panniculitis are more common then the generalized form. In the past, most solitary lesions in the cat where thought to be idiopathic. Today, we know that they can be a sign of a vaccine or drug reaction which might "go" to fibrosarcoma. Diagnosis of panniculitis is easily made by cytology but the true diagnosis requires surgical removal with wide margins.

Idiopathic Sterile: Although rare cases of dietary steatitis still are reported, this cause of panniculitis are rare. True cases of primary, generalized panniculitis are very rare in the cat.

Infectious: Recurrent "idiopathic panniculitis" lesions on the ventrum or at the site of previous wound or surgery should be evaluated carefully for atypical

mycobacterial, Nocardial, or other bacterial infections. Aspiration cytology for culture is reported to be more effective then biopsy techniques. Regardless of the organism isolated, treatment is long and problematic, especially in atypical mycobacteroisis. In that disorder, Baytril® (11-22 mg/kg q24h - CAREFUL OF BLINDNESS) can be effective but not all cases will respond. If an initial response is seen, treatment must be continued until all lesions disappear (eyes and fingers) and then for at least two more months. Premature cessation of treatment predisposes to relapse. For resistant cases, clofazimine (8-12 mg/kg/q24h) has been successful in some cases. Detailed reading on the drug (CVT12) should be done before treatment is undertaken.

PERFORATING DERMATITIS

Some cats appear to develop abnormal areas of collagen in their superficial dermis. Instead of developing an eosinophilic granuloma at the site, these cats eliminate the damaged collagen through their epidermis. The clinical lesions are very well circumscribed crusty lesions. Diagnosis by biopsy. Vitamin C (100 mg/q12h) may be of some benefit.

ACTINIC DERMATITIS

Lightly pigmented cats will develop an actinic dermatitis if they are allowed to bask in the sun. In cloudy climates (Ithaca!!), it takes years for the dermatitis to develop. Even if the sun bathing is abruptly stopped at the first sign of change, the dysplastic cells will persist and may continue their transformation to full-fledged tumor cells (squamous cell carcinoma). In most cases, the solar exposure can't be stopped completely and tumor will develop. The pliseotherapy, strontium 90 β irradiation, used in Bowen's disease works very nicely to eradicate the dysplastic cells.

FELINE SARCOID

A recently describe tumor of predominantly young cats with a rural background. One or more lesions especially on the nose, face, ear, feet, and tip of the tail. Slow growing but incomplete excision accelerates growth rate. Resembles equine sarcoid in its histology and biological behavior but no viral etiology show here (yet). Wide surgical excision is curative.

PLASMA CELL PODODERMATITIS

Still a disorder with an unknown pathomechanism. The majority of cats have no systemic involvement and experience one episode in their lives. When the cat is ill, myeloma must be considered. Cat with recurrent or recalcitrant disease should be checked for FIV.

Since some (many?) cases undergo spontaneous resolution, the determination of a successful treatment is difficult. If the cat can be housed indoors on a soft carpet, no treatment is needed. When the pads ulcerate, infection is present (cause or result of the ulceration?) and needs to be treated for typically 30 days. Cats crippled by their disease or subject to recurrent infection will respond to high levels of prednisolone (4.4 mg/kg q24h) or other immune modulators. Healed pads may remain somewhat soft due to scarring deep in the pad.

FELINE CLAW DISORDERS

Beyond traumatic avulsion of an individual claw, claw disorders, especially those involving multiple claws on multiple paws, are rare in the cat Unlike the dog where disorders of the claw itself are fairly common, cats tend to present with paronychial involvement. In the author's practice, the paronychia usually is sterile and secondary to pemphigus, systemic lupus, or drug eruption. Bacterial disease, when

present, usually is superimposed on some sterile disease but primary bacterial paronychia does occur in immunosuppressed cats.

Destructive paronychia, a condition when the paronychial skin is ulcerated, is more common in the cat then dog. Thrombi lodge in the vessels of the digital skin blocking blood flow with subsequent tissue necrosis. The most commonly recognized condition involves thrombosis from an asymptomatic bronchogenic carcinoma.

ULCERATIVE DERMATITIS WITH LINEAR SUBEPIDERMAL FIBROSIS

This condition was reported in the early 90's as an idiopathic condition of the cat. It remains so today. Affected individuals develop spontaneous erupting crusted ulcers over the dorsal neck and shoulder area. The lesion usually is not pruritic but will not heal. Surgery is curative.

Once removed, this lesion has no significance. Since the site of involvement is in a vaccine zone, the tissue should be sent for histologic evaluation where it can be differentiated from a vaccine-induced panniculitis.

MILIARY DERMATITIS

The most common crusting skin disorder of the cat is miliary dermatitis. In the early era of feline dermatology, miliary dermatitis was thought to be a specific disease entity. Today, we know that miliary dermatitis is a reaction pattern in the cat and not a specific disease. Diseases seen within this reaction pattern include:

Bacterial folliculitis	Dermatophytosis	Otodectes
Cheyletiella infestation	Feline scabies	Pediculosis
Demodicosis	Trombiculosis	Fur mite infestation
Nutritional deficiency	Flea allergy	Atopy
Food allergy	Insect allergy	Pemphigus
Lupus	Drug reaction	EM/TEN
Mast cell disease	FIV infection	Idiopathic

Diabetic Ketoacidosis

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Diabetes Mellitus was first reported in a cat in 1927 and is now recognized as a fairly common endocrine disorder. Diabetes mellitus results when insulin secretion by pancreatic beta cells is impaired, or when tissue cells are resistant to the action of insulin. In both situations the body's ability to regulate glucose metabolism is impaired. Insulin deficiency accounts for the fasting hyperglycemia seen in this disorder. Severe deficiency also results in marked glucose overproduction and excessive mobilization of the body's protein and fat stores.

Diabetic ketoacidosis (DKA) results from an absolute or relative insulin deficiency in conjunction with glucagon and stress hormone excess. It is crucial to identify underlying disease factors contributing to stress in these patients. Stress factors include changes in environment, dehydration and concomitant disease. Commonly associated diseases include feline hepatic lipidosis, renal disease, urinary tract and other infection, and pancreatitis. DKA is characterized by hyperglycemia, dehydration, ketonemia, metabolic acidosis and multiple electrolyte abnormalities. Treatment must be intensive and directed towards the correction of fluid, electrolyte and acid-base abnormalities as well as the correction of abnormal carbohydrate metabolism. Without treatment DKA is fatal and it should be considered a medical emergency. The mortality rate for DKA is 25-30 %, even with aggressive treatment.

Clinical Signs

Clinical signs seen in cats with ketoacidosis include polyuria, polydipsia, weight loss, anorexia, vomiting, diarrhea, lethargy, weakness, dehydration, obtundation and hyper- or hypoventilation. These clinical signs may develop in various combinations and are usually severe in the ketoacidotic cat.

Diagnostic Work-up

A. Laboratory tests
    a. Immediate PCV, TS, BUN and blood glucose
    b. CBC, Chemistry panel
    c. Venous or arterial blood gas analysis
    d. Serum electrolytes
    e. Serum osmolality
B. Imaging tests
    a. Chest radiographs
    b. Abdominal radiographs
    c. +/- Abdominal Ultrasound
C. Urinalysis, including culture and sensitivity

Fluid, Acid-base and Electrolyte abnormalities

Hyperglycemia causes an osmotic diuresis, predisposing to dehydration. Excessive fluid loss can lead to severe hypovolemia, with associated hypotension, compromised tissue perfusion, and lactic acidosis. Ketonemia further compounds the metabolic acidosis. DKA patients also suffer total body depletion of potassium and phosphorous due to anorexia and osmotic diuresis. Magnesium is also lost into the urine and severe hypomagnesemia may be associated with a refractory hypokalemia.

Treatment

A. Fluid Therapy

The fluid of choice is an isotonic solution such as 0.9% sodium chloride, lactated Ringer's solution or Plasmalyte-A. 'Shock' doses (20-40 ml/kg) of fluids may be required in cases of severe hypovolemic shock or acidosis. In more stable patients, fluid requirements should be calculated to restore hydration over 10-12 hours.

B. Correction of Metabolic Acidosis

Metabolic acidosis may correct following intravenous fluid and insulin therapy via oxidation of ketone bodies and excretion of hydrogen ions in the urine. In cases of severe acidosis (pH < 7.1; TCO2 < 10 mEq/l) judicious administration of sodium bicarbonate is recommended in order to improve cardiac contractility and peripheral vascular tone. The estimated dose of $NaHCO_3 = 0.3 \times BW_{kg} \times (18\text{-serum } HCO_3)$. One quarter of the deficit is administered intravenously over 20 minutes; the remainder is administered in intravenous fluids over 4-6 hours. Side effects of sodium bicarbonate therapy include decreased serum potassium concentrations and hyperosmolality.

C. Correction of Electrolyte Abnormalities

a. Potassium: Serum potassium levels may decline precipitously following fluid and insulin therapy. Clinical signs include marked skeletal muscle weakness (as evidenced by poor neck muscle tone), paralytic ileus, respiratory paralysis and cardiac arrhythmias. Supplementation of intravenous fluids with Potassium Chloride (KCl) is essential.

Potassium replacement*:

Serum K (mEq/l)	KCl /L fluids (mEq)	Max. rate (ml/lb/hr)
3.6-5.0	20	12
3.1-3.5	30	8
2.6-3.0	40	5.5
2.1-2.5	60	4
< 2.0	80	3

* Rate of supplementation should not exceed 0.5 mEq/kg/hr

b. Phosphorus: Hypophosphatemia may develop following insulin therapy due to intracellular shifting of phosphorus. Hypophosphatemia causes skeletal muscle weakness, hemolytic anemia and respiratory failure, due to decreased 2,3DPG and ATP levels in active tissue and red blood cells. If phosphorus levels decrease below 1.8 mg/dl or CPK levels are high (> 1500), phosphate replacement is indicated. Potassium phosphate may be dosed as an intravenous constant rate infusion of 0.01-0.03 mmol/kg/hr, for 12-24 hours. Serum phosphorus concentration must be monitored closely during therapy. Over supplementation may cause hypocalcemia.

c. Magnesium: Hypomagnesemia has been associated with the development of refractory hypokalemia. In these cases, magnesium supplementation can be provided intravenously, using magnesium sulfate at a dose of 1 mEq/kg/day.

D. Insulin therapy

Regular, crystalline insulin is the insulin of choice in DKA. It may be administered intravenously or intramuscularly.

a. Intravenous insulin

If given intravenously, insulin is diluted in isotonic saline solution and administered as a constant rate infusion at a dose of 1.1 U/kg/24 hr. If the total daily dose of insulin is placed in 240 mls of saline, is can be infused at a rate of 10 ml/hr. When provided intravenously, insulin acts rapidly to lower the blood glucose level and frequent monitoring is recommended.

b. Intramuscular insulin

Alternatively, regular insulin may be administered by the intramuscular route. It is used hourly at a dose of 0.1-0.2 U/kg until blood glucose concentration decreases to less than 300 mg/dl. At that point, insulin frequency can be reduced to every 6 hours and it may be administered intramuscularly or subcutaneously (if the patient is well hydrated). Blood glucose monitoring should be hourly initially, but may be measured every 2-4 hours once the frequency of insulin administration decreases.

c. Supplementation with dextrose

It is important to note that the metabolism of ketones requires insulin. If the blood glucose level drops into the normal range, but ketonemia persists, insulin therapy must be continued. This necessitates the supplementation of intravenous fluids with dextrose, in order to prevent the onset of hypoglycemia. The continued supplementation of dextrose

provides a carbohydrate substrate that enhances the metabolism of ketones.

d. Long term insulin therapy

Once the patient is well-hydrated and no longer ketoacidotic, subcutaneous insulin injections can be initiated. Regular insulin may be used at a dose of 0.5-1 U/kg; Long acting insulin (NPH, Lente or Ultralente) may be dosed at 0.5 U/kg.

Insulin CRI - Therapy Adjustments

If glucose is:	**Fluids +/- dextrose**	**Insulin (1.1 U/kg/day)**
> 250 mg/dl	Isotonic fluid	10 ml/hr
150-250 mg/dl	IV fluid + 2.5 % dextrose	10 ml/hr
100-150 mg/dl	IV fluid + 5% dextrose	5 ml/hr
< 100 mg/dl	IV fluid + 5% dextrose	Stop insulin infusion

E. Antibiotic therapy is indicated in the presence of systemic infection or fever.

References

Available upon request.

Transfusion Medicine

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Blood transfusions play a critical role in the management of cats with anemia, bleeding disorders and hypoalbuminemia. The transfusable components of blood are erythrocytes, leukocytes, platelets, coagulation factors and albumin. Historically veterinarians have relied on in-house donor cats as a source of blood for transfusion purposes. Blood was collected for immediate use and sophisticated collection and storage techniques were not well developed. The growing need for transfusions has led to advances in collection and storage techniques as well as to the development of large blood donor programs in veterinary institutions. More recently, commercial animal blood banks have been successful in the marketing of blood products to veterinary practitioners.

Blood typing and Cross matching

Blood types are genetic markers on erythrocyte surfaces that are antigenic and species specific. Two or more blood types make up a blood group system.

The only blood group system recognized in cats is the AB blood group system. This consists of three blood types: type A, type B and type AB. Type A is the most common blood type; type B is more common in certain breeds such as Persian, Himalayan, Abyssinian, Birman, Scottish fold, Somali, British shorthair and Devon Rex cats; type AB occurs extremely rarely. A simple blood typing card is available to classify cats as type A, B or AB.

Blood cross matching tests discover the serologic compatibility or incompatibility between donor and recipient; they test for the presence or absence of naturally occurring and induced alloantibodies in serum or plasma. A major cross match tests for alloantibodies in the recipient's plasma against donor cells, whereas a minor cross match test looks for alloantibodies in the donor's plasma against the recipient's red blood cells. A major cross match incompatibility predicts that the transfused donor cells will be attacked by the patient's plasma, causing a potentially life-threatening transfusion reaction.

In contrast to dogs, cats have naturally occurring alloantibodies against the blood type antigen they lack. Type A cats have weak anti-B alloantibodies, which cause a shortened survival of transfused B cells in type A cats. Type B cats possess strong anti-A antibodies and a mismatched transfusion will result in fatal acute hemolytic transfusion reaction. If blood typing is not available, a cross match should be carried out prior to any transfusion in a cat.

Blood component therapy

Indications for the use of fresh whole blood include anemia, excessive hemorrhage and bleeding disorders (related to platelet or clotting factor deficiencies). Stored whole blood has the same indications but is less useful in the treatment of coagulation abnormalities. Whole blood transfusions are still the most common form of blood transfusion therapy in feline medicine.

Separation of blood into its cellular and plasma components allows for more efficient replacement of the patient's needs. Component therapy also reduces the likelihood of transfusion reactions resulting from unnecessary cellular or plasma protein administration. Selection of appropriate components also reduces the likelihood of volume overload following transfusion therapy in an anemic, but euvolemic, patient.

Whole blood can be separated into the following components: packed red blood cells (PRBC) and whole plasma. Plasma may be further classified as fresh, stored, frozen, or fresh-frozen plasma (FFP). Further plasma derivatives can include cryoprecipitate and platelet-rich plasma, although these are not used in feline medicine at this stage.

Packed red blood cells are prepared by removing plasma from a unit of whole blood. They are suspended in anticoagulant and preservative additive solutions and stored at 1-6°C. The shelf life varies from 21 to 35 days. Packed red cells are used in anemic patients, to increase oxygen carrying capacity, where there is no need for platelets or clotting factors. After separation of red cells from the unit of blood, the remaining plasma is frozen. This fresh frozen plasma contains coagulation factors and may be used to treat patients with acquired or congenital coagulation disorders. It may also be used in severely hypoproteinemic patients in order to raise recipient serum albumin concentrations.

While component therapy is ideal for meeting specific patient requirements, in feline medicine it has proven difficult to achieve due to the difficulty with the creation of closed and sterile blood collection systems. However, academic institutions and commercial blood banks are beginning to use and supply packed red cells and plasma.

Rate of administration

1) Whole blood or Packed Red Blood Cells: 10 ml/kg, over 1-4 hours; may give more rapidly in hemorrhagic shock
2) Plasma: 10 ml/kg, over 1-2 hours

Whole blood and packed red blood cells should be administered after slow warming to 37°C. Blood administration sets containing filters are commonly used; these filters remove blood clots and other particles.

Transfusion Reactions

Blood transfusions can produce various adverse reactions, ranging from allergic urticaria to life-threatening hemolytic reactions. The severity of most transfusion reactions is dose dependant; early recognition of a problem can avert disaster. Patients should be carefully observed, particularly during the first 30 minutes of the transfusion.

Cats with type B erythrocytes have strong, naturally occurring anti-A antibody. These cats will have strong, acute and often fatal transfusion reactions if given type A blood. Fewer than 30% of type A cats have anti-B antibodies, and type AB cats have no preformed antibodies to blood types. If type A cats receive type B blood, a slow transfusion reaction may result in an abbreviated donor red cell life span, thereby reducing the effectiveness of the transfusion.

Monitoring parameters include measurements of temperature, heart rate, pulse strength and synchronicity, and respiratory rate. These parameters should be monitored 15, 30 and 60 minutes into the transfusion. If a reaction is suspected, the transfusion must be stopped immediately. Clinical signs associated with transfusion reactions include fever, vomiting, facial edema, hemolysis, tachypnea, urinary and fecal incontinence, tremors and shock. Severe reactions are rare when patients have been correctly typed and cross-matched.

The benefit of the prophylactic use of antihistamines and glucocorticoids has been debated. Pre-treatment with 0.5 mg/kg of diphenhydramine administered intramuscularly or subcutaneously, may reduce the risk of acute hypersensitivity reactions. However, there is no published literature supporting this at this time. Glucocorticoids do not acutely suppress the production of IgG or IgM antibodies and therefore are not considered to be useful in prevention of transfusion reactions.

Blood donor programs

Incentive Plan

a. Free vaccinations (Rabies, FVRCP, FeLV) (yearly)
b. CBC, Biochemistry Profile, Feline Leukemia, FIV, and hemobartonella screening (yearly)
c. Blood typing
d. Free blood transfusion if ever becomes necessary
e. 8-10 pound bag of cat food with each donation

Annual health screen

a. Laboratory screening (CBC, Profile, FeLV, FIV, hemobartonella)
b. Physical examination.
   Cats with abnormal lab work, heart murmurs or abnormal heart rhythms are excluded from the donation program.
   Caution: In some cases "sub-clinical" heart disease can be missed, particularly in cats.
c. Minimum weight requirement (8 pounds)
d. Age range of 1 to 10 years

Donation Procedure

Unlike dogs, cats require sedation/anesthesia to donate. As with dogs, owners will leave their cat at the hospital for the day. Each cat receives a complete physical exam prior to donation. Cats are sedated with a ketamine/diazepam mixture or anesthetized using an inhalant anesthesia (isoflurane). Blood is obtained from the jugular vein and the entire donation process takes about 10-15 minutes. Cats are offered a high calorie meal following donation and are observed for any problems. Most cats are discharged within 2 hours of donation.

Alternatives to Blood Transfusion: The use of Oxyglobin

Despite the growth of commercial animal blood banks and blood donor programs at large veterinary centers, blood products remain a limited resource. Additionally, despite the advances in species-specific blood typing and cross matching techniques, transfusion reactions still occur.

Corporate research has focused on the development of hemoglobin solutions, as alternatives to blood transfusion. Because hemoglobin solutions lack red blood cell antigens, there is no need for cross matching and blood typing. In January 1998 the FDA approved a hemoglobin-based oxygen-carrying solution (Oxyglobin, Biopure, Boston, MA) for use in dogs. This solution consists of hemoglobin polymers, has low viscosity and is isosmotic. The product can be stored at room temperature for up to two years. When administered to a patient, it increases plasma and total hemoglobin concentration and thus increases arterial oxygen content. Its oxygen affinity is lower than that of canine and feline blood, thereby enhancing oxygen delivery to tissues. The enhanced oxygen content and delivery permits efficient tissue oxygenation without increased cardiac work.

Oxyglobin has a variety of clinical indications for the emergency veterinary patient. It has been used in cases of hemolytic anemia, thromboembolic disease and vascular obstruction, postoperative hemorrhage, with variable success. Side effects include the potential for volume overload, mild vomiting and diarrhea. The mucous membranes, sclera and urine become discolored after treatment. Discoloration of serum will also interfere with the results of certain laboratory tests such as serum creatinine, serum bilirubin and coagulation parameters.

The use of hemoglobin based oxygen carriers such as Oxyglobin is worth considering in anemic patients. The dose range for dogs is 15-30 ml/kg; however the high

end of the range should be avoided in euvolemic patients. The rate of administration should not exceed 10ml/kg/hr in dogs. Although the solution has not been approved for use in cats, a lower dosage of 3-5ml/kg has been proposed. Cats receiving Oxyglobin should be very closely monitored for signs of volume overload.

There have been questions raised about serious side effects such as volume overload, pulmonary edema and hypertension, particularly in the feline species. Further clinical evaluation is necessary before the complete picture is evident. In the meantime, Oxyglobin is a useful addition to our arsenal of emergency treatments in anemic and hemorrhaging patients.

References

Available upon request.

FELINE HYPERTHYROIDISM: 6000 CATS AND COUNTING

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In 1979, my favorite cat, Boo, lost weight, developed a ravenous appetite, had an unkempt coat and had daily episodes of vomiting. She had had a cholecystoduodenostomy performed 2 years before and developed subsequent mild liver enzyme elevation and frequent biliary calculi. A complete work-up failed to identify her problem. She was hospitalized while I went to visit my parents for Christmas. A veterinary student suggested that a serum T_4 be done. Her T_4 was "off-the-scale". As soon as I returned home, a thyroid scan confirmed bilateral thyroid tumors. Boo had a hemithyroidectomy done and barely survived the surgery. At that time she weighed 4 pounds. Thus began my goal to use radioiodine to destroy the remaining thyroid tumor tissue and Boo became the first cat treated with radioiodine for hyperthyroidism at UC Davis.

Hyperthyroidism, originally described in 1979 by Jean Holzworth, is currently the most common endocrine disease of the cat and is caused by multinodular adenomatous hyperplasia, functional adenomas or functional carcinomas of thyroid tissue. Histologically, it is difficult to differentiate these 3 forms. Thyroid adenomas involve both lobes, 70% of the time and one lobe, 30% of the time. Malignant thyroid tumors (usually involving one lobe) have a prevalence of 3 to 5%. The age range of affected cats is 4 to 22 years with an average age of 14 years. Diagnosis of hyperthyroidism is usually straightforward. A history of weight loss and increased appetite, physical examination findings of an enlarged thyroid gland, rapid heart rate and weight loss, and a high serum thyroxine concentration are features we all would like to see to make the diagnosis of this condition. In reality, there is a broad spectrum of historical findings and clinical signs that many cats are presented with and diagnosis is more difficult. We have suspected from the first descriptions of this disease that its etiology was dietary induced and a recent publication has confirmed this.

Historical and Clinical Findings

Weight loss is the most common and predominant finding; sometimes only a few ounces are lost and in other cats, over 50% of body weight can be lost in a relatively short period of time. Weight loss of more than a few ounces in older cats is important and should be investigated. Obese cats with hyperthyroidism placed on reducing diets are often undetected because weight loss is encouraged and only until the cat overshoots the weight reduction goal will the cat be presented. Many cats are not presented until weight loss is marked because owners think the cat is "just getting old". Typically, a brisk to ravenous appetite is observed with cats changing from finicky eaters into vocal scavengers for food.

Increased incidence of vomiting is commonly seen and is usually related to a higher presence of hairballs, increased intestinal motility, or voracious appetite causing gastric distension. Stools may have a fetid odor, change to a pale gray color, and become voluminous. The frequency of defection is increased. Occasionally, stools will progress to diarrhea.

Polydipsia and polyuria are frequently noted clinical signs. Many cats will double water consumption and seek unusual sources of water (jumping into the bathtub or sink to drink from

the faucet or swimming pool). Some owners notice the need to change the litter pan more frequently because of the increased urine present.

Behavior and personality changes are seen in 20 to 30% of affected cats. Hyperactivity and restlessness characterize classical signs of hyperthyroidism. Most owners reject the concept of hyperactivity until it is pointed out to them that it is unusual for an older cat to be awake for more than a few hours a day. On presentation, hyperthyroid cats are difficult to control because of increased activity. Some cats develop an aggressive attitude, often attacking and biting. Other cats will become more affectionate and seek more attention. Inappropriate defecation and/or urination have been reported. The owner may report that the cat is frequently hiding in unusual locations within the house or become withdrawn. Some cats will change sleeping locations from sunny or warm areas to cool bare floors or shady areas because of the increased peripheral circulation. One striking sign associated with this disease is increased vocalization, oftentimes when the cat is alone in a room (owners describe these cats as "senile"). Sometimes cats with other diseases will destabilize, such as those inflammatory bowel disease, diabetes mellitus or heart disease.

The apathetic form of hyperthyroidism is seen in approximately 10% - 15% of hyperthyroid cats and is marked by signs of poor to no appetite, dehydration and emaciation, and marked lethargy and weakness. These may or may not be preceded by the classic signs of hyperthyroidism.

Physical Examination Findings

Palpation of the thyroid gland is an essential part of the physical examination and should be performed on all cats regardless of age. The normal thyroid gland is a bilobed structure located on either side of the trachea just caudal to the larynx with no connecting isthmus. These 2 lobes are not palpable in normal cats. Most cats with hyperthyroidism have at least one palpable thyroid lobe. Frequently one lobe is larger than the other is; the larger lobe usually gravitates caudally into the ventral cervical region. Markedly enlarged thyroid lobes may be located within the thoracic inlet or even in the cranial mediastinum. The disease is not always bilateral so both sides of the trachea should be carefully palpated. To properly palpate the thyroid gland, place the cat in a standing position with the head and neck extended vertically. The thumb and index finger should be placed on either side of the trachea at the thoracic inlet and gently slid toward the larynx. Enlarged thyroid lobes will slip under the finger/thumb as the hand is advanced cranially.

Thyroid tumors may elude palpation because of their location dorsolateral to the trachea, gravitation of tumors through the thoracic inlet into the cranial mediastinum, or inexperience of the veterinarian. Therefore, hyperthyroidism cannot be ruled out based on palpation. Conversely, palpation of one or two thyroid lobes is abnormal and should be investigated further.

Integumentary changes include an unkempt, greasy, easily matted hair coat. The owners often note excessive shedding. Occasionally cats will pull hair out in clumps while grooming. Excessive shedding and grooming are more common and a change in hair coat color to reddish or brownish tinged hair can be seen. Longhair cats previously easily groomed are commonly presented with heavily matted coats. Ears and feet feel warm because of peripheral vasodilatation. Excessively long toenails are common.

A variety of cardiac abnormalities including tachycardia, premature beats, gallop rhythm, and systolic murmurs are seen in cats with hyperthyroidism. In one study only 30% of

hyperthyroid cats had normal cardiac function. Other signs include a pronounced pounding heartbeat, dyspnea and panting. Approximately 50% of cats with hyperthyroidism will have radiographic evidence of cardiomegaly. Echocardiographs will show hyperdynamic function of the myocardium rather than cardiomyopathy. Those cats with concurrent cardiomyopathy and hyperthyroidism may show signs of heart failure including pleural or pericardial effusion and pulmonary edema.

Other clinical signs are moderate to severe gingivitis and dental disease (reflecting the degree of debilitation) and difficulty in being handled due to hyperactivity and aggressiveness. Abdominal palpation will often show small kidneys due to concurrent kidney disease. Cats that urinate during examination should be evaluated for urinary tract infections. And finally, some cats will show few clinical signs and are remarkably healthy.

Recent studies have shown that a majority of hyperthyroid cats are also hypertensive (> 160 mm Hg). Clinically, signs of hypertension include pounding heart, venous distention, polyuria/polydipsia, tachycardia, and small kidneys. Hypertension usually occurs when cats have both hyperthyroidism and kidney disease. Blood pressure should be measured when the cat is well hydrated.

Serum Thyroxine Concentration (T_4) Testing

The most reliable and widely used test for diagnosing feline hyperthyroidism is total serum T_4 concentration determination. Total T_4 is a combination of free and protein-bound thyroxine concentrations. Each laboratory has established normal ranges for their particular assay and therefore normal values are not interchangeable between laboratories. Hyperthyroid cats may have total T_4 concentrations 30 times higher than normal or they may have total T_4 concentrations in the high normal reference range. Typically, older euthyroid cats have normal T_4 concentrations near the lower half of the normal reference range. Total thyroxine concentrations in the middle or high end of the reference range are abnormal for older cats. When found in conjunction with one or two palpable thyroid nodules, a free T_4 should be done to confirm the diagnosis.

Serum T_4 concentrations fluctuate from day to day and hour to hour with variations found to be greater over a 15-day period than over a 10-hour period. The degree of fluctuation can result in a normal serum T_4 concentration once and a high serum T_4 concentration the next time. Routine testing of T_3 is not helpful or warranted.

Some cats have clinical signs of hyperthyroidism before serum T_4 concentrations are above the normal reference range. Systemic non-thyroidal diseases of several days' duration can also lower serum T_4 concentrations. Some medications such as cortisone, NSAIDS, trimethoprim-sulfa, and anticonvulsants will lower total T_4. In these cases; a free T_4 by equilibrium dialysis is the more reliable test. The T_3 suppression test and TSH or TRH stimulating tests are not used much at this time. No assay for determining TSH concentrations of cats exists at this time.

Technetium-99m Pertechnetate Thyroid Scanning

The most reliable procedure for establishing the diagnosis of hyperthyroidism in cats is the technetium-99m (^{99m}Tc) pertechnetate thyroid scan. The test is simple and easily performed.

Approximately 3 to 5 mCi of ^{99m}Tc is injected subcutaneously. This radioisotope is trapped in the iodine-seeking tissues of the body (thyroid gland, salivary glands, and gastric mucosa). Enough trapping of this radioisotope is completed after 20 to 60 minutes to image the body using a gamma camera. Normal thyroid lobes and the salivary glands should accumulate approximately the same amount of ^{99m}Tc and so should be approximately the same size and intensity on the scan image. Findings typical of hyperthyroidism are increased uptake in the thyroid gland relative to the salivary tissue and increased thyroid lobe size. Failure to visualize thyroid tissue occurs when cats are fed dietary supplements, diets or supplements high in iodine (kelp), or have been given organic iodide preparations to control signs of hyperthyroidism. Antithyroid drugs do not interfere with performing a thyroid scan.

From the scan images, one can determine whether one or both thyroid lobes are involved, the relative size of the affected thyroid lobes, presence of functional ectopic thyroid tissue, and whether the tumors are benign or malignant. In the presence of unilateral thyroid lobe involvement (30%), the only thyroidal uptake will be by the affected side. The normal contralateral lobe will be atrophied and so will not trap ^{99m}Tc (not visible). The vast majority of cats will have bilateral thyroid adenomas (70%); some have both lobes affected to the same extent (symmetric) and some will have one lobe much larger than the other (asymmetric). Ectopic thyroid tissue is rarely seen in hyperthyroid cats because its tissue will be atrophied unless a functional tumor is also present in that ectopic tissue.

The incidence of thyroid carcinomas is approximately 5%. These carcinomas appear as multiple nodules distributed throughout the neck and cranial mediastinum. Other sites of metastases (lung, liver, and bone) from functional malignant thyroid tumors are usually functional and so can easily be found on the scan. Malignant non-functional thyroid tumors are rare and will not trap radioisotope. In some of these cats, the opposite thyroid lobe may have functional benign tumors. Cats that have had thyroidectomy with recurrence of clinical signs will often have multiple "hot spots" reflecting fragmentation of the residual thyroid tumors adherent to the thyroid capsule. These scans are impossible to differentiate from cats with thyroid carcinoma.

Many facilites treating cats with radioiodine do not perform thyroid scans. I believe that it is an invaluable source of information. Approximately 50 to 75 cats each year are sent home untreated because the thyroid scan was negative. In those cases repeat total and free T4's confirm that the cats are not hyperthyroid and that the original tests were in error. Secondly, cats with thyroid carcinomas can be identified and the correct dose of radioiodine can be given. Finally, the thyroid scan is used to help individualize the best estimated radioiodine dose for each cat.

Laboratory Abnormalities

Although several changes have been noted on serum chemistry profiles of hyperthyroid cats, the only consistent ones are mild to moderate elevations of liver enzymes (serum alkaline phosphatase, serum alanine aminotransferase, and serum aspartate aminotransferase). Liver enzyme elevations are related to the high metabolic rate of the cat and usually are not caused by pathologic changes in the liver. Typically, the only hematological changes are a mild leucopenia and mild hemoconcentration. The urinalysis should be normal with a specific gravity of > 1.035.

Renal disease often occurs simultaneously in cats with hyperthyroidism and may or may not be caused by the hyperthyroidism. Since most cats with hyperthyroidism are older, pre-existing renal disease may be exacerbated by the metabolic changes of hyperthyroidism. Some

cats will develop renal failure, possibly due to hypertension. Biochemical changes of these cats are low urine specific gravity, high normal to high blood urea nitrogen, high normal to high creatinine, and high serum phosphorus levels. The presence of compensated kidney disease does not preclude radioiodine treatment.

Differential Diagnosis and Concurrent Diseases

Many other diseases can occur which either mimic the signs of hyperthyroidism or can occur simultaneously and be obscured because of the similarity of signs. Diabetes mellitus, chronic renal disease, inflammatory bowel disease, pancreatic insufficiency, cardiomyopathy, and hypertension are the most common diseases producing at least some signs similar to feline hyperthyroidism. Most of the signs of these diseases will be exacerbated by even mildly elevated serum T_4 concentrations. Elimination of hyperthyroidism will often result in easier control of these concurrent diseases or allow them to go into remission. Cats with previously diagnosed cardiomyopathy should be re-evaluated 3 months after treatment for hyperthyroidism to re-assess the diagnosis and the need for medication.

Other diseases with a less optimistic outlook need to be discovered before the cat is given definitive treatment for hyperthyroidism. These include lymphoma of the abdominal viscera, other neoplasms of the viscera, oral tumors, lung disease (cats don't cough), severe renal disease, and congestive cardiomyopathy. Unfortunately, a search for unknown neoplasms can be cost prohibitive as well as delaying treatment for hyperthyroidism. In those cases, underlying diseases may only surface after effective treatment for hyperthyroidism has been done. Oral medication to control the hyperthyroidism is worthwhile so that the work-up for the more occult disease can be continued.

The best strategy for detection of concurrent diseases is a complete physical examination including examination of the oral cavity for infection, dental disease, and neoplasia, careful auscultation of the heart and lungs and thorough palpation of the abdominal cavity. A complete blood count, serum biochemistry profile and urinalysis are the minimum database. Abdominal and thoracic radiographs may be indicated based on the physical examination findings. Further testing may include examination of the abdomen by ultrasound and the heart by ultrasound or electrocardiogram.

One of the most important rules of hyperthyroidism and concurrent disease is that there must be a direct relationship between the degree of illness in the cat and the level of thyroid hormone concentrations. Emaciated cats with an only slightly elevated T_4 should tell you that something else is seriously wrong.

Initial Treatment

After the diagnosis of hyperthyroidism has been made, the owner should be advised regarding the appropriate treatment. If the cat is seriously ill with either hyperthyroidism alone or with concurrent disease, I prefer to treat both diseases, the one with radiodioine and the other appropriately. There are others who prefer that the cat be stabilized before definitive treatment is undertaken. In most cases when the cat is asymptomatic or is in stable condition, definitive treatment should be scheduled as soon as possible.

Antithyroid drugs are indicated for cats seriously ill with hyperthyroidism but caution must used when making that decision. Approximately 25% of cats will develop side effects to these drugs. Propylthiouracil and methimazole are most commonly used to counteract thyroid production. Methimazole is used more frequently because it produces fewer side effects. Both drugs act by preventing thyroid hormone synthesis and can result in a return to euthyroidism in 1 to 2 weeks. The initial dose of methimazole is 2.5 –5 mg orally bid to tid but is dependent on the T_4 concentration. The T_4 concentration should fall into the normal range within 2 weeks. If it does not, the dose should be regulated appropriately. Similarly, the cat's medical condition should also stabilize. If it does not, another reason for the cat's illness should be searched for. Cats that are stable at this time should be referred for radioiodine treatment or thyroidectomy.

It should be noted that, regardless of treatment modality selected, if tachycardia or other cardiac arrhythmias are present, beta-blockers should be prescribed. Antihypertensive drugs, antibiotics, and kidney disease management may have to be instituted as well.

Radioiodine Treatment

Radioiodine treatment is acknowledged as the safest, most effective treatment and is the treatment of choice for feline hyperthyroidism. Radioiodine (^{131}I) has a half-life of 8 days and emits a spectrum of beta and gamma radiations. Iodine is actively trapped and incorporated into the functional thyroid tumors but does not accumulate in atrophied normal thyroid tissue. Therefore, normal thyroid tissue as well as the parathyroid glands and other surrounding tissues are spared the effects of irradiation.

The dose of ^{131}I activity administered is based on the serum T_4 concentration, the size of the thyroid tumor on palpation and thyroid scan, and whether the tumor appeared benign or malignant on the thyroid scan. Other considerations are the cat's other medical problems and inherent body metabolism. Activities of ^{131}I administered for benign tumors range from 1 to 8 millicuries and are given subcutaneously; the dose of ^{131}I for malignant tumors is much higher and ranges from 15 to 25 millicuries. Cats on antithyroid drugs must have the drug stopped for 4 to 5 days before treatment. Otherwise ^{131}I uptake is lowered and excretion is accelerated increasing the likelihood for a second treatment. Some cats are so fragile that they cannot be removed from antithyroid drugs before treatment; in those cases, ^{131}I is given at a higher dose to counteract the effects of these drugs.

As rules for radioiodine usage have become less rigid in some states, radioisotope licenses have been granted to numerous veterinary hospitals. Hyperthyroid cats can be readily transported to these referral centers. The procedure for scanning and treatment takes only a few hours. Some referral centers have gamma cameras but most treat cats based on Palpation and T4 levels. Doses of radioiodine are either determined as a fixed dose ranging from 4 to 10 mCi depending on the facility. In other facilities, doses are individualized but without the benefit of a scan. The risk for cats becoming hyperthyroid by either method is high.

Within one to two days after treatment, cats improve clinically and feel much better. By the time the cats are discharged, thyroid hormone levels are usually in the normal range. Cats treated with radioiodine are usually hospitalized for 4 to 14 days (depending on the radiation safety rules of the state they are treated in) so those radioactive excreta can be collected. This hospitalization period is in sharp contrast to humans treated with radioiodine who can go home the same day.

The major disadvantage of ^{131}I treatment is the hospitalization time required. No side effects from the treatment are present. Normal thyroid tissue and parathyroid glands are spared and normal thyroid function returns within 1 month after treatment. During this recuperative period, some cats will be sluggish, have a decreased appetite, and appear to sleep more than usual. These signs gradually lessen as thyroid hormone concentrations return to normal.

Cats with thyroid carcinoma given therapeutic doses of radioiodine will have complete ablation of all thyroid tissue and will require thyroid supplementation and frequent monitoring to ensure tumor control. Long-term tumor control and good quality-of-life are the usual results after radioiodine treatment of thyroid carcinoma. Only rarely will cats succumb to recurrent or persistent malignancy. In some cases, the residual thyroid mass remains and may need to be excised if it persists longer than 6 months.

Approximately 5% of cats given an individualized dose (dose selected for the tumor and the cat) require a second treatment to eliminate the tumor. Another 5 % of cats will develop hypothyroidism after radioiodine treatment; this can easily be treated with thyroxine supplementation. Recurrence of hyperthyroidism after successful treatment is rare, occurs 2 to 8 years after initial treatment, and is usually associated with a malignant thyroid tumor.

Thyroidectomy

If radioiodine treatment is not selected for one reason or another, the other treatment alternative is thyroidectomy that can be done by practitioners with reasonable surgical skills. Ideally, a thyroid scan should be performed before surgery to identify which thyroid lobes are involved and the location of that tissue. Only then can an informed decision be made on which thyroid tissue needs to be removed. In reality, few cats are scanned before thyroidectomy and the decision to remove 1 or 2 lobes is based on thyroid lobe appearance at the time of surgery.

Unilateral thyroidectomy, usually done by the extracapsular method, is performed in those cats which have unilateral thyroid tumors as identified on ^{99m}Tc thyroid scan or by inspection of the thyroid lobes at surgery. Since only 1 lobe is removed, the likelihood of the cat becoming hypothyroid or hypocalcemic is low. The major disadvantage of this technique is that the probability of the opposite lobe having or developing adenomatous tissue is high, approaching 80%.

Bilateral thyroidectomy, usually now performed using the modified intracapsular/extracapsular technique, is done when both lobes are affected. The intracapsular technique involves peeling the thyroid tissue from the capsule to leave intact the blood supply to the parathyroid glands. The modification is that the parathyroid glands located at the cranial poles are undisturbed by leaving the capsule around that tissue (extracapsular). Regardless of the surgical procedure used, all tissue should be submitted for histopathology. Examination of the tissue will determine if thyroid tissue was removed (occasionally lymph nodes are removed instead of thyroid tissue), whether parathyroid glands are present in the sample, and if thyroid tissue is benign or malignant. If a diagnosis of malignancy is given, a thyroid scan should be performed soon after surgery to identify if the tumor has metastasized to lymph nodes and lungs. If metastases are found, high-dose radioiodine treatment is indicated.

Intraoperative complications include damage to the vagosympathetic trunk causing Horner's syndrome, damage to the laryngeal nerve causing laryngeal paralysis, damage to the

esophageal nerves causing megaesophagus, and uncontrolled hemorrhage. Occasionally both thyroid lobes cannot be found despite lengthy dissection usually due to gravitation of the larger lobe into the thoracic inlet. A few cats will have neoplastic ectopic thyroid tissue in the cranial mediastinum which is also difficult to retrieve. In both situations, these cats will remain hyperthyroid after surgery.

The most serious post-operative complication is disruption of the blood supply to the parathyroid glands resulting in hypocalcemia. This situation is life-threatening and occasionally despite intensive treatment for hypocalcemia can be fatal. Serum calcium levels should be monitored daily for 4 to 7 days after bilateral thyroidectomy. If the serum calcium concentration falls below 7.0 mg/dl, the cat may show signs of hypocalcemia including restlessness, facial pruritis, ear twitching, abnormal behavior, muscle tremors, tetany, and convulsions.

The other serious complication of thyroidectomy is loss of normal thyroid hormone production. If a unilateral thyroidectomy is done and the remaining thyroid lobe is normal, serum T_4 concentrations will return to the normal range over the ensuing month due to stimulation of the atrophied thyroid tissue's response to TRH and TSH. When bilateral thyroidectomy is done, serum T_4 concentration will be low and the cat should be supplemented with thyroxine at a dosage of 0.1 mg/cat once daily. In the vast majority of cats having bilateral thyroidectomy, clinical signs of hypothyroidism will not develop. This is either due to stimulation of ectopic thyroid tissue to produce T_4 or, perhaps more commonly, production of thyroid hormones by residual thyroid tumor cells adhering to the thyroid gland capsule. Over a long enough time, these cells will once again produce excessive levels of thyroid hormones. Serum T_4 concentrations should be routinely monitored every 6 months on cats having any thyroidectomy procedure. If a cat becomes hyperthyroid after having a total thyroidectomy, radioiodine treatment should be done because the likelihood of hypocalcemia increases greatly with subsequent surgeries.

Long-term Medical Management

A few hyperthyroid cats are not good candidates for either radioiodine treatment or surgery because of either concurrent disease or advanced age (> 20 years). Some clients refuse definitive treatment for a wide variety of reasons citing that these procedures are either too stressful, too risky, too expensive, etc. Regardless of the reason, the only other treatment alternative is continuous medical management with antithyroid drugs. Generally, methimazole is given at a dosage of 5 mg/cat bid to tid. As the tumor enlarges, the dose of methimazole must be increased. Frequent monitoring of T_4's and CBC's should be done to ensure proper dosage and to detect hematologic abnormalities. Cats should not be kept on antithyroid drugs for longer than 6 months. Beyond that time, owner compliance is diminished, the risk of side-effects is increased, the need to increase the dose and frequency of administration is increased, and the cost effectiveness begins to equal the cost of either radioiodine treatment or thyroidectomy.

Several disadvantages of these drugs are readily apparent. Antithyroid drugs do not affect the growth of the thyroid tumor and so as the tumors grow, more drug must be given. Antithyroid drugs must be given at least once to three times daily for the remainder of the cat's life in order to control clinical signs. Periodic T_4 concentration determinations and a complete blood count (every 2 weeks for 3 months) should be done to insure that the correct dosage of drug is given and that toxic bone marrow effects or autoimmune disorders are not developing. 25% of cats on antithyroid drugs will suffer from mild to fatal side-effects. Methimazole is less toxic than propylthiouracil but both drugs can cause similar side-effects. Thyroid carcinomas are

seen in cats on long-term methimazole due to malignant transformation of the previously benign adenomas.

Side-effects associated with antithyroid drugs include anorexia, vomiting, dehydration, lethargy, and skin rashes/excoriations or alopecia. More severe side-effects are the hematologic complications that can be life-threatening. They include the presence of antinuclear antibodies, Coombs' positive hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia. Side-effects are more likely to occur in the first 3 months of treatment but can develop at any time. If side-effects occur, then withdrawal from the drug should be done immediately and supportive care for the side-effects should be done. The decision to perform definitive treatment must be reconsidered at this time.

Treatment Sequel

Cats receiving definitive treatment for hyperthyroidism generally have dramatic improvement in health and will regain normal behavior, appetite, and physical appearance within 1 to 2 months after treatment. In the first few weeks after treatment several important physiologic changes are occurring which need to be identified and monitored. Cardiac changes are dramatic with return to normal heart rate and rhythm. An important sequel to these cardiac changes is a lowering of blood pressure (80% of cats have high blood pressure before treatment). Lowered blood pressure results in a reduction of the glomerular filtration rate by approximately 25%. This drop can be significant in cats with early renal disease and precipitate decompensated renal failure. These cats need to be managed with either oral or subcutaneous fluid supplementation, low-quantity, high-quality protein diet, calcium supplementation to increase available calcium in the gastrointestinal tract, and other supportive therapy. Intensive and aggressive treatment and careful monitoring of these cats must be done until the kidneys have readjusted to the physiologic changes.

Heart failure can result after hyperthyroidism is corrected, mostly due to loss of stimulus to the heart and residual hypertension from the concurrent renal disease. Hypertension and/or cardiac drugs must be given until these problems resolve.

Another important finding is that some cats will not return to their weight and predicted good health. Monthly rechecks for the first 3 months should be done to assess physical status and to monitor T_4 concentrations. If the cat does not gain weight, then an aggressive search for an underlying disease must be done. The most common problems are decompensated renal disease, cardiomyopathy, or a second neoplasm.

It is the balance of "compensatory" increases in single nephron GFR with the development of glomerulosclerosis that will determine total kidney GFR (and to what magnitude the BUN and serum creatinine will increase with advancing renal lesions). It often seems inevitable that once chronic renal failure is diagnosed that it invariably gets worse (more renal lesions accumulate or further renal functions are lost). It is not possible to predict the rate of this progression in experimental or clinical animals. Figure 4. displays several possible scenarios that may be observed during the course of chronic renal failure.

Figure 4 -A. Linear Decline in Excretory Renal Function

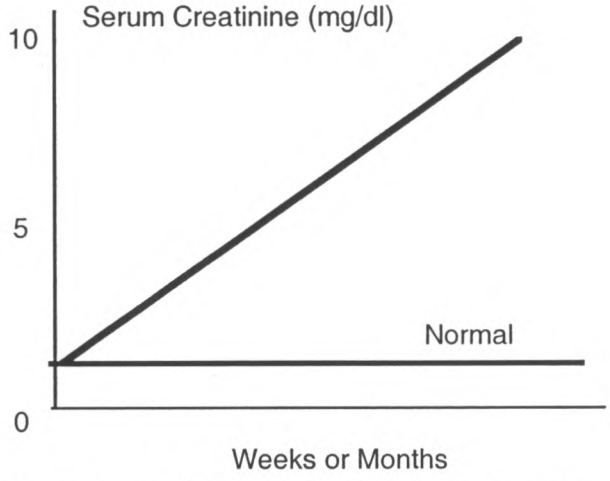


Figure 4-B. Episodic Decline in Excretory Renal Function

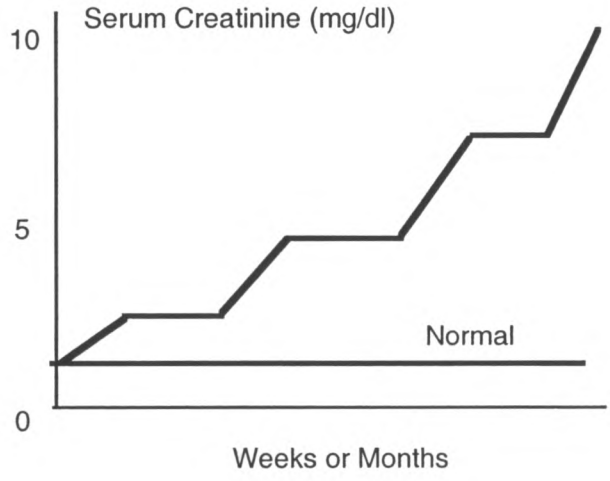


Figure 4-C. Prolonged Periods of Stable Excretory Renal Function After Initial Decline

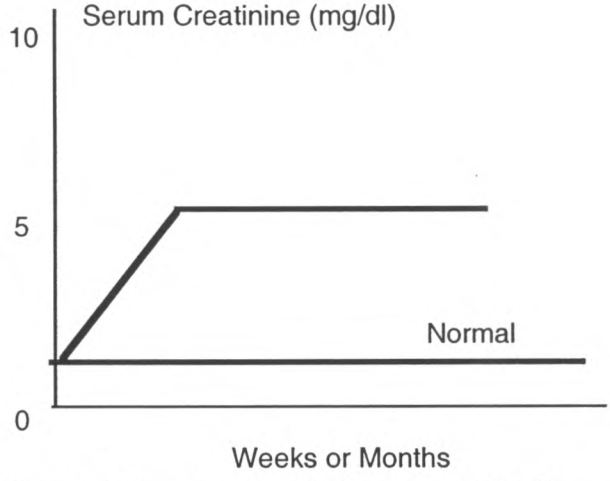
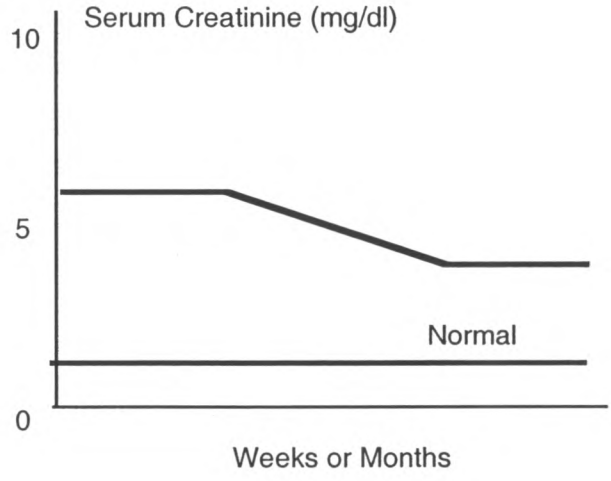


Figure 4-D. Increased Excretory Function After Initial Decline



Dennis J. Chew, DVM, ACVIM; The Ohio State University College of Veterinary Medicine 2000

Figure 5-A. Increased Concentrations of Serum Creatinine Due to Acute Pre-Renal Factors (No Further Lesions or permanent hemodynamic changes have occurred within the kidneys)

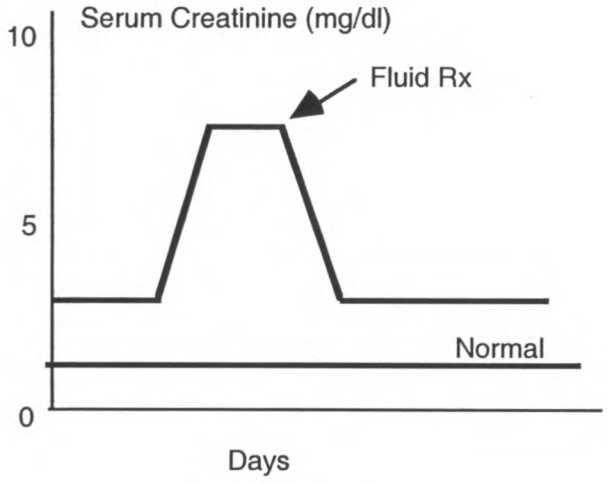
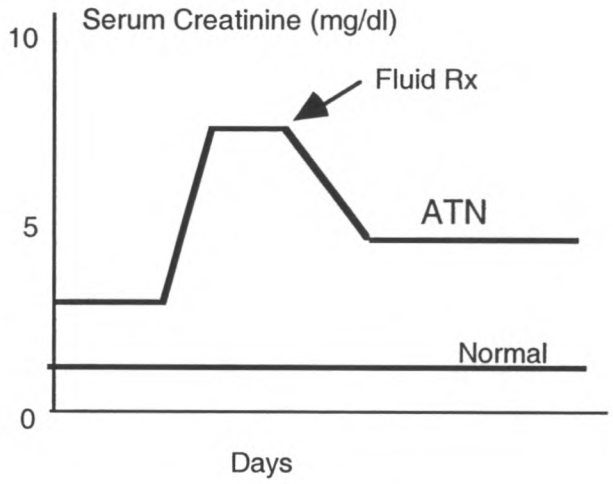


Figure 5-B. Increased Concentrations of Serum Creatinine Did Not Return to the Original Baseline Due to Acquisition of Acute Renal Failure Lesions (Acute Tubular Necrosis).



Though the lesions of CRF are permanent, reversible factors that reduce renal function or contribute to further development of renal lesions can exist on top of CRF. These include dehydration, hypoadrenocorticism, anesthesia and surgery, heart failure, urinary tract obstruction, urinary tract infections, leptospirosis, hypercalcemia, hypokalemia, pyometra, heartworms, systemic lupus erythematosus, endocarditis, ehrlichiosis, Rocky Mountain Spotted Fever, and borreliosis (?).

CATS WITH CHRONIC RENAL FAILURE (CRF) - HOW DIFFERENT THAN CRF IN DOGS ?

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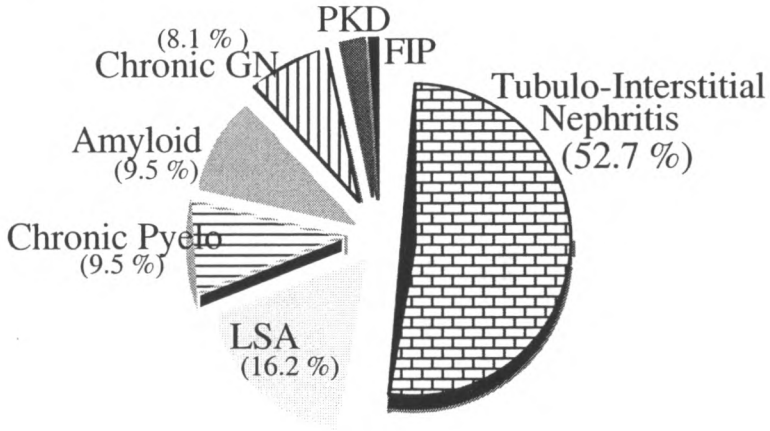
Frequency of Chronic Renal Failure in Cats

Chronic renal failure is common in cats and its prevalence is apparently increasing. As many as 15 to 30 % of cats over the age of 15 have CRF. This increase in the detection of CRF in cats could be due to an actual increase in the frequency of this disorder or possibly due to increased veterinary attention to aging cats. Cats less than 3 years of age uncommonly have CRF; increased risk for CRF has been seen in cats greater than 7 years old.

Differential Diagnoses

Tubulo-interstitial nephritis of unknown cause accounts for the number one diagnosis of CRF in the cat, as in the dog. Cats have several renal diseases that deserve extra consideration compared to that in dogs.



Glomerulonephritis and Renal Amyloidosis

Primary glomerular disease appears to be less common in cats than in dogs as a cause for endstage renal disease. Chronic antigenemia from FeLV or FIV should be considered as a possible underlying cause in cats with glomerulonephritis. In Abyssinian cats amyloidosis appears to be familial, probably a dominant trait with variable penetrance (DiBartola). Renal amyloid occurs sporadically in non-Abyssinian cats. There is extreme variability in the age of onset and the severity of renal involvement. Amyloid is preferentially deposited in the renal medulla and to some degree in glomeruli in 75% of affected cats. Proteinuria is a less reliable indicator of renal amyloidosis in cats than in dogs (non-Shar Pei) due to variable glomerular involvement in cats. Since biopsies sample tissue from the cortex, medullary amyloid deposits will be missed and glomeruli may not contain amyloid obscuring the diagnosis. Biopsy may reveal changes of chronic interstitial nephritis and fibrosis associated with amyloid deposits.

Polycystic Kidney Disease and Renal Lymphoma

Polycystic kidney disease (PKD) is an important consideration in Persian and other longhair cats, whereas this is extremely uncommon in dogs. A variable number of cortical and medullary cysts continue to increase in number and size with age in affected cats leading to progressive loss of functional renal mass occupied by the cysts. Chronic tubulointerstitial nephritis is also associated with the renal cysts. All cats with PKD have at least one parent also affected with PKD (autosomal dominance inheritance). Renal ultrasonography is the imaging method of choice to confirm PKD. Renal biopsy is not necessary. Renal cysts may be seen with ultrasound in some affected cats as early as 7 weeks of age; the absence of detectable cysts by 6 months of age usually indicates that the cat is not affected with PKD. Enlarged non-painful kidneys are often detected on abdominal palpation. Irregular protrusions are palpable from the kidneys of some PKD affected cats, while other cyst enlargements appear smooth and symmetrical.

Bilateral renal lymphoma resulting in CRF is much more likely in cats than dogs. Renal LSA is a major differential for enlarged kidneys in the cat, both smooth and irregular on palpation or with renal imaging. The kidneys may be the only organ documented with LSA infiltration. Feline leukemia virus status is often negative when the kidney is the only organ affected with lymphoma. Fine needle aspiration of renal tissue and cytology is usually adequate to diagnose renal LSA. Chemotherapy may be effective in lessening the degree of renal failure when neoplastic lymphocyte infiltration is diminished.

Urinary Tract Infection (UTI)

UTI in cats with chronic renal failure appears much more commonly than in cats with lower urinary tract disorders. UTI in cats with chronic renal failure appears to be more common than that encountered in dogs with chronic renal failure. The reasons for this remain to be determined but could be related to loss of a protective effect conferred by maximal urinary concentrating capacity during advancing renal disease. Alternatively, diseased renal tissue may be more readily colonized by bacteria(acquired pyelonephritis). A third possibility is that upper urinary tract infections may be the initial cause for loss of renal function.

Hyperthyroidism

The effects of hyperthyroidism on renal function and renal disease in cats have not been fully characterized. Since cats with CRF and hyperthyroidism tend to be older, it is difficult to assess a possible interaction between these two disorders. It is likely that hyperthyroidism is underdiagnosed in cats with chronic renal failure since nearly half of cats with CRF and hyperthyroidism will have a normal T4 level on a single measurement. It has been noted by us and others that a population of hyperthyroid cats develop azotemia or display a worsening of azotemia following therapy to induce euthyroidism. It is known that thyroid hormones have a supportive role for GFR through its effects to increase renal blood flow. It is possible that lessening the degree of hyperthyroidism results in decreased RBF and GFR which unmasks azotemia in cats with marginal renal function prior to therapy. GFR decreased while BUN and serum creatinine increased in a group of cats which underwent bilateral thyroidectomy as

treatment for hyperthyroidism (Graves). Some cats in this study developed overt renal azotemia. Some increase in serum creatinine concentration are expected following the development of euthyroidism due to increased muscle mass (origin of creatinine). Similar findings have been observed in some cats in which euthyroidism was achieved following methimazole or I-131 radiation treatments (DiBartola).

Hyperthyroidism is known to result in dilute urine and polyuria with polydipsia. This effect is likely due to increased RBF and medullary solute washout, though a direct effect on the collecting tubules and ADH receptor interaction cannot be excluded. Psychogenic mechanisms also cannot be excluded. Hyperthyroidism is known to result in hypercalciuria in other species due to enhanced bone calcium mobilization; this effect may have some role in the development of polyuria as well as a possible role in creating chronic renal damage by excessive exposure of renal tissue to calcium. Most cats with hyperthyroidism also have increased systemic blood pressure which could injure renal tissue.

Should cats with overt azotemia and hyperthyroidism be treated for hyperthyroidism ? It is likely that many of these cats will increase their level of azotemia following treatments that result in euthyroidism. In some cats this increase in creatinine will be mild, while other cats will experience large increases in serum creatinine. If clinical signs related to hyperthyroidism are severe, at attempt at treatment is warranted. We recommend screening cats with obvious azotemia and those suspected of renal disease with a methimazole challenge. Methimazole treatment provides a reversible means of inducing euthyroidism and observing what happens to the level of renal function. An initial dose of 2.5 mg BID is given for 2 weeks and then serum biochemistry is repeated to evaluate renal function and T4 levels. If renal function is stable, the dose is gradually increased every two weeks as needed until T4 levels have entered the normal range if renal function remains stable. The dose can be increased to 2.5 mg TID, then 5 mg BID, and 5 mg TID if needed. Methimazole is discontinued if renal function deteriorates during the methimazole challenge. If renal function remains stable, then long term methimazole can be considered for therapy or more-definitive treatment of hyperthyroidism provided by I-131 treatment or surgery. The definition of "stable" renal function is arbitrary and in our hospital means that the creatinine increased less than 2.0 mg/dl in those without initial azotemia and less than 1.0 mg/dl in those with obvious azotemia. Supplementation with thyroxine should be considered for those cats with renal disease that become hypothyroid following definitive treatment.

Potassium Depletion Nephropathy

A syndrome of chronic renal failure and severe muscle weakness has been observed in clinical and research cats fed acidifying diets that were marginally replete with potassium, decreased in magnesium, and high in protein content. This syndrome has been referred to as potassium depletion nephropathy or kaliopenic nephropathy, though it occurs in a setting with other complex nutrient modifications. Chronic hypokalemia can cause functional renal lesions (e.g. defective urinary concentrating ability, decreased GFR), structural renal lesions, and chronic renal failure, but the exact mechanisms remain unknown. Chronic renal failure appears to be the most common condition associated with hypokalemia in general populations of sick cats.

The question remains of whether potassium depletion and hypokalemia occur prior to the development of CRF as a possible cause or as an effect after CRF develops. Truncal ataxia with a "hanging head" is an effect of severe potassium depletion and hypokalemia. This type of severe manifestation is now much less common as pet food manufacturers have increased potassium supplementation of their diets. It is possible that subclinical potassium depletion may be important in cats with CRF that develop weight loss, lethargy, anorexia, poor quality of hair coat and anemia ; usually these problems are blamed on advancing renal failure. Potassium supplementation to cats with hypokalemia and CRF has been described to have many beneficial effects on general well-being as well as on improved renal function. A beneficial effect of potassium supplementation to cats with CRF and normal serum potassium concentration remains to be shown, but anecdotes do support this use. A recent study at OSU (Theisen) failed to show a beneficial effect on renal function of potassium gluconate vs sodium gluconate supplementation to cats with chronic renal failure and normokalemia.

History

Lethargy, anorexia, and weight loss are the most common signs in cats with CRF. Polyuria and polydipsia are detected by owners in less than half the cases, in contrast to most dogs. Vomiting is reported in about 30-50% of cats with CRF. Inappropriate location for urinations are uncommon in cats with just CRF.

Physical Exam

Dehydration and emaciation are the most common findings detectable on physical examination. Oral ulcers occur occasionally, but less so than in dogs. Tongue-tip necrosis, as seen in uremic dogs, is very rare in cats with CRF . Small and irregular kidneys are palpable in about 25 % of cats with CRF. About 25 % of cats with CRF will have palpably enlarged kidneys, higher than that encountered in dogs. Nearly two-thirds of cats with CRF display systemic arterial systolic hypertension when assessed by Doppler and occlusive cuff methods. Retinal lesions are occasionally encountered especially during severe hypertension (retinal detachments, hemorrhages), observed in as many as 4 to 5 % of cats with CRF.

Table 1). **Differential Considerations for Renomegaly in Cats**

1. Lymphoma (LSA)
2. Granulomatous Nephritis -FIP/Toxoplasmosis
3. Hydronephrosis
4. Polycystic Kidney Disease (PKD)
5. Perinephric Pseudocyst
6. Acute Primary Renal Disease
   - Pyelonephritis
   - Acute Tubular Necrosis
7. Intact Male Kidneys
8. Compensatory Hypertrophy -Unilateral

Chronic Renal Failure (CRF) : Renal Lesions and Nature of Progression

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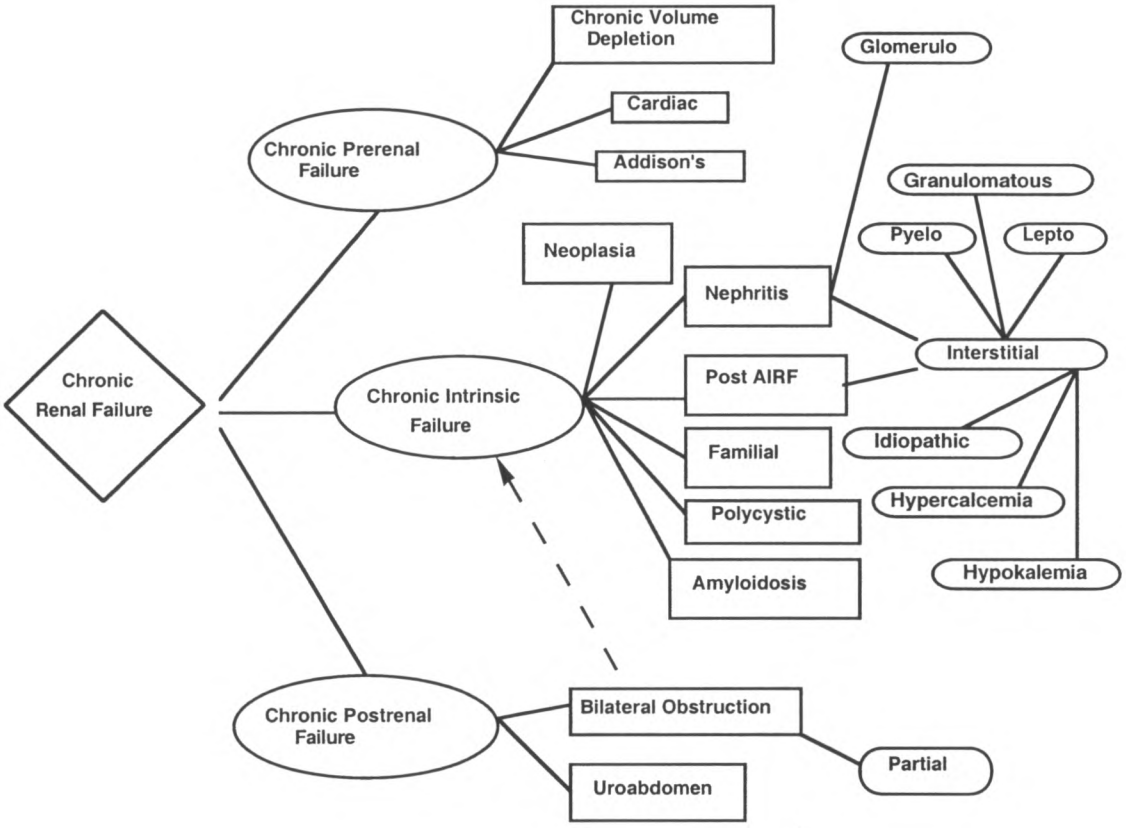
Chronic primary (intrinsic) renal failure (CRF) is not a specific diagnosis, but rather the endpoint of a variety of generalized vascular, glomerular, interstitial, and /or tubular disease processes (see Figure 1). Accurate diagnosis is essential in order to construct a therapeutic plan likely to be of any benefit.

Figure 1. Potential Causes for Chronic Azotemia, including Chronic Pre-Renal, Chronic Post-Renal, and Chronic Primary-Renal

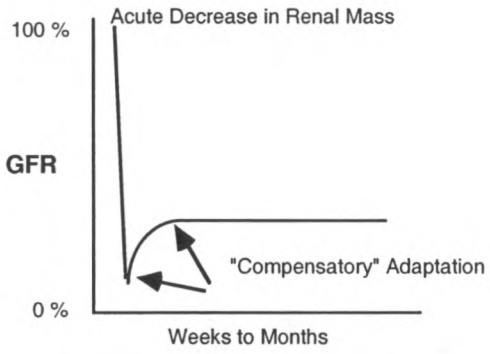


Progression of Chronic Renal Failure

CRF is clinically characterized in dogs and cats by the development of variably progressive irreversible intrarenal lesions and loss of renal functions (sometimes referred to as " the inexorable progression of chronic renal failure"). It is not known for certain why progressive loss of renal function and development of renal lesions occur in CRF. The original cause of the renal injury may still be present(as in pyelonephritis or renal amyloidosis). Most often an underlying cause for the initial renal insult cannot be found yet progressive renal injury with loss of function continues. It appears that a critical mass (threshold or "trigger-point") of nephron loss is necessary before self-perpetuating mechanisms continue to destroy remaining viable nephrons. "Super-nephrons" that result from hypertrophy of renal function and

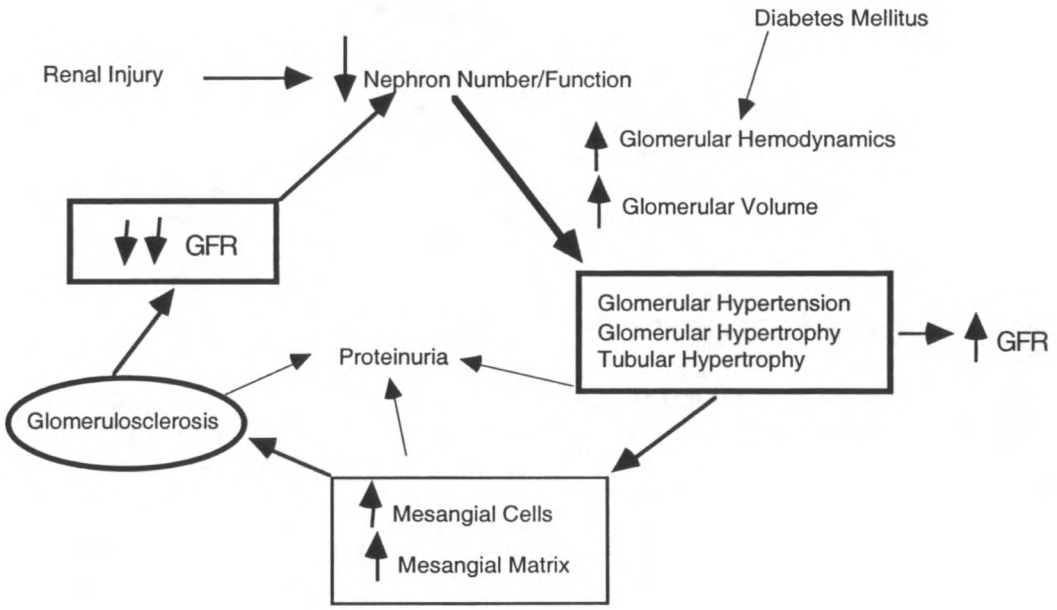
increased glomerular volume in remaining viable nephrons may result in their eventual demise.

Figure 2. Compensatory increase in single-nephron GFR following decreased total kidney GFR. Following major reduction in total kidney GFR, some remaining nephrons increase their GFR; the signal for this increase is not known.



Hemodynamic adaptations cause increased single nephron GFR, glomerular plasma flow, and increased transglomerular capillary hydraulic pressure that are initially adaptive to maintain excretory function and increased total kidney GFR. It is possible that this intraglomerular hypertension and increased glomerular volume eventually harm glomeruli however, as shown in Figure 3. Tubular hypermetabolism, hyperammoniagenesis, renal mineralization, systemic arterial hypertension, intrarenal coagulation, and immune mechanisms may also contribute to chronic progressive renal injury.

Figure 3. Compensatory increases (adaptations) in glomerular hemodynamics and glomerular volume may actually be maladaptive in some instances as shown in this figure.



Urinalysis

About 10 % of clinical cats with CRF retain their ability to concentrate urine to greater than 1.025 specific gravity. Isosthenuria(1.007-1.015) is encountered in about 60% of cases, while moderate urine concentration from 1.016-1.025 is seen in about 30% of cases. When urine specific gravity is less than 1.035, the presence of renal disease should be suspected in cats, especially when dehydrated. 50% of cats with CRF have mild to moderate (+1 to +2) proteinuria based on dipstrip reactions. Hyaline and granular cast can be seen in nearly half of cats with CRF. It is likely that many cats with CRF will display diagnostically relevant microproteinuria as evaluated with the urinary protein to creatinine ratio.

Treatment of Cats with CRF

Most treatments for cats with CRF are similar as for dogs with CRF (dietary modification, phosphate restriction, H-2 receptor blockers). Dietary protein restriction to about 20 % of calories from protein are presently recommended by our nephrology and nutrition service. Since most commercial cat foods are acidifying, these foods should be discontinued and either a non-acidifying prescription catfood provided or a homemade diet fed. Cats with experimental CRF due to subtotal nephrectomy experienced fewer lesions of glomerulosclerosis in remnant tissue when fed diets restricted in protein and calories, compared to those that were not restricted. GFR and degree of proteinuria were higher in those cats fed the high protein/calorie diet, but GFR did not change in either feeding group over a one year study period (Adams and Polzin).

Subcutaneous Fluids

Subcutaneous fluids administered at home can be well-tolerated by the cat and owner for long times. Fluids such as Lactated Ringer's solution can be given at 100-200 ml daily as needed daily, every other day, or only during times of stress.

Hypokalemia

Hypokalemia occurs more commonly in cats than in dogs with CRF and is most likely to occur at presentation in those with polyuric renal failure, especially when anorexia is present. Hypokalemia is much more common than hyperkalemia in cats with CRF. Hypokalemia may also develop after rehydration with potassium-deficient fluids, during periods of spontaneous diuresis, and during periods of intensive therapeutic diuresis.

An initial oral doses of 3-8 mEq/day of potassium is given to those cats with mild hypokalemia; often the dose is tapered to 2-4 mEq/day for chronic maintenance. Potassium supplementation at 10 to 20 mEq/L of can be given in fluids for cats receiving subcutaneous fluids at home.

Metabolic Acidosis

Potassium citrate or potassium gluconate may provide correction of acidosis as well as additional potassium that may be of benefit. Sodium bicarbonate is generally avoided as an alkalinizing agent because of the potential for the sodium component to exacerbate systemic arterial hypertension believed to be common in cats with CRF. Uremic acidosis can contribute to increased dietary protein needs encountered in CRF.

Human Recombinant Erythropoietin (EPO)

The use of EPO to combat hypo-proliferative anemia of CRF is more financially attractive for use in cats due to their small size in general as compared to dogs. The use of EPO is generally restricted to cats with PCV less than 20 % due to the possible development of anti-EPO antibodies in as many as 60 to 70% % of cats exposed to this human product. Clinically significant anti-EPO antibody formation usually takes place within 30 to 90 days after starting treatment if it is going to be a problem. Severe anemia and dependence on transfusions may be prolonged - anti-EPO antibodies likely cross react with native endogenous EPO.

Renal Transplantation

Renal transplantation has achieved a degree of success in cats with chronic renal failure greater than that experienced in dogs. Cyclosporine and prednisolone provide adequate immunosuppression to allow allograft survival for extended periods in some cats (Gregory and Gourley). A high degree of surgical skill is required for successful anastomoses of small vessels and ureteral implantation into the bladder. Vascular thrombosis or stenosis, ureteral stenosis, and uroabdomen are all complications related to the degree of technical difficulty encountered during this surgery. Cases most likely to be candidates for successful transplantation are those without other systemic diseases, without severe hypertension, without urinary or other organ system infections, and those in which uremic lesions throughout the body are not too severe. Successful renal transplantation as replacement therapy for CRF in cats requires a unique team of talented surgeons and veterinarians specially skilled in immunology.

Chronic Renal Failure (CRF)- Dietary Treatment in the Compensated Patient

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Dietary modification and nutritional support are important parts in the overall management of patients with CRF. Treatment will depend on the animal's degree of compensation toward CRF. Animals that are asymptomatic or have mild signs (minimal weight loss, slight decrease in appetite, occasional vomiting, mild anemia, not dehydrated) are treated on an outpatient basis. Animals with decompensated CRF have more severe signs/problems including vomiting, anorexia, depression, moderate to severe anemia, dehydration, electrolyte, and acid-base disorders that may require hospitalization for initial stabilization (see Uremic Crisis).

An ideal diet for dogs and cats with CRF would accommodate decreased renal functional reserves, minimize formation of uremic toxins, decrease obligatory urine volume in those with polyuria, optimize food intake and nutritional status, avoid diet-related problems, optimize the animal's quality of life, and delay or prevent the progression of renal disease. This may be asking too much for any one diet to do - this ideal diet has not yet been developed. Indeed, it is likely that no one dietary formulation will be able to take care of the needs of all animals with CRF depending on individual differences as well as stage of renal disease.

It is important to distinguish between factors that can contribute to the quality of an animal's life from those that can prevent progressive loss of renal function. It is possible that dietary factors that improve an animal's sense of well-being have nothing to do with preservation of renal function. The factors which might contribute to progression of CRF have been under intense study for the past 20 years (most information has been in dogs with more recent studies in cats). Emphasis for study has traditionally been on the role of dietary protein which recently has been supplanted by those emphasizing phosphorus. Despite many studies, it remains difficult to separate with certainty just how important individual nutrient formulations contribute to the progression of CRF, though much has been clarified as regards protein and phosphorus(further below).

Management of Anorexia

Chronic uremia frequently is associated with poor appetite due to a combination of central depression from uremic toxins, GI ulceration, stomatitis and oral ulcers, and/or lingual necrosis. An altered sense of smell/taste during uremia may also be contributing to anorexia. Foods that are designed for the treatment of CRF are often restricted in protein, phosphorus, and salt which may make them less palatable in general. Aversion to foods that were associated with hospitalization or forced feedings can also contribute to anorexia.

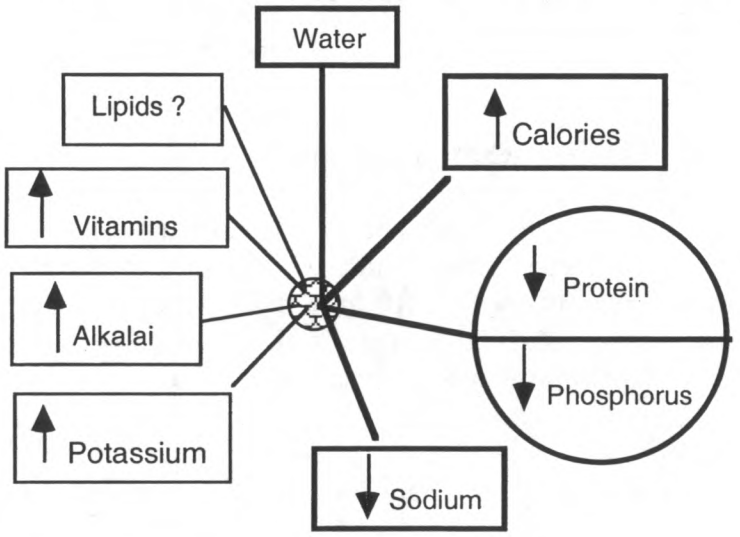
Cimetidine, ranitidine, and famotidine (H-2 receptor blockers) can be useful to treat gastric ulcers/gastritis when administered to uremic dogs and cats to reduce gastric acid secretion. Increased gastrin concentration in serum during CRF (decreased renal degradation)is believed to be responsible for stimulation of gastric acid over-secretion and ulcer formation. Some uremic dogs and cats dramatically increase their food intake and interest in food after starting one of

these drugs. Some uremic animals may need this medication for an extended period of time (months to the rest of their lives). Much of our experience has either been with cimetidine at an initial dose of 10 mg/kg followed by 5 mg/kg PO BID or famotidine (Pepcid®) at 1 mg/kg once daily. Omeprazole(proton pump blocker in stomach) is an alternative to the H2-receptor blockers for its effect to decrease stomach acid, but we have little experience in its use during CRF. It can be considered for use in those in which H-2 receptor blockers were not effective in the control of vomiting.

Metoclopramide (Reglan®) may be useful in uremic animals that vomit or show signs of nausea (excessive liplicking, swallowing, drooling). It works partly by depressing the CTZ emetic center in the brain and also by enhancing gastric emptying. We usually have used this in those patients in which H-2 blockers were ineffective, though some recommend its use as the first-line agent of choice. It can be given orally at 0.2 to 0.4 mg/kg TID to QID and may be most effective if given about 30 minutes before a meal. Sucralfate (Carafate®) as the "gastrointestinal band-aid" may be useful to coat painful GI ulcers and promote increase food intake. We usually administer sucralfate to those that have melena from GI bleeding.

Flavors added to protein-restricted food can enhance their appeal and intake, including small amounts of bacon drippings, hamburger grease, chicken drippings, tuna juice, clam juice, or baby food. Some animals will increase their intake of protein-restricted foods if the food is prewarmed in the microwave or fried (ala burgers). Offering a variety of commercially available diets designed for the treatment of CRF (Vet's Choice, Hills, Waltham, Vet Kem, , Iams, Innovative Veterinary Diets) may allow the pet to select one that it will consume to the greatest degree. Home-made protein and phosphorus restricted diets may be consumed by the pet with CRF when commercial foods will not be eaten. Multiple small volume meals with special diets should be attempted in an effort to avoid overdistension of the stomach and nausea or vomiting that might be encountered during CRF.

Figure 1) Hierarchy for Dietary Modification Consideration During CRF



Water and caloric intake are the first priorities while designing dietary modifications for dogs and cats with CRF. Fresh water should be available at all times to encourage maximal hydration. Adding water or flavored broths to dry foods may encourage more water intake than otherwise. Some animals maintain better hydration when fed canned foods rather than dry foods, an effect attributed to the greater amount of water that is available for intestinal absorption. Adding water to dry food in a 1:1 volume ratio may also provide additional water to help maintain hydration.

Caloric intake is pivotal toward the ultimate success or failure of a dietary regimen. Adequate caloric intake is essential to turn off the balance of catabolic forces that are so often operative in patients with CRF. In the absence of adequate caloric intake, catabolism is enhanced as insulin secretion is diminished at a time that glucagon secretion is enhanced. When dietary protein restriction is prescribed, it is imperative to ensure adequate non-protein calories at the time of protein intake ; otherwise the protein will be degraded for energy and not utilized by the body while generating more nitrogenous waste products for accumulation throughout the body.

Dietary Protein Restriction

Mild to moderate dietary protein restriction with high quality protein at a time of generous non-protein caloric intake remains a cornerstone treatment in the management of stable CRF (after decompensated CRF has been stabilized if necessary) Since many uremic solutes are generated following protein degradation, dietary protein restriction may be beneficial in alleviation of uremic signs associated with moderate to severe azotemia. Moderate azotemia is defined as a BUN > 70 mg/dl and a serum creatinine > 2.5 mg/dl in the hydrated state. It is important to establish post-rehydration BUN and serum creatinine concentrations as the baseline for evaluation as to whether protein restriction is likely to "make the animal feel better". It is unlikely that protein restriction in patients with lower baseline concentrations of increased BUN or serum creatinine will be able to enjoy the salutary effects of protein restriction, since their starting points for uremic waste products is marginal. Protein restriction has the potential to result in generation of less uremic solute, phosphorus, and acid for excretion. Lower protein intake can result in generation of less urea for excretion into urine which reduces the magnitude of obligatory polyuria and secondary polydipsia, a tremendous benefit to some clients. Obligatory polyuria is a function of the level of renal function and of the solutes requiring renal excretion.

Is it a bad idea to recommend mild dietary protein restriction for those with confirmed primary renal disease but that are not yet in obvious excretory failure? Examples of such cases would include those with normal BUN and serum creatinine, submaximal urinary concentration, proteinuria on dipstrip, increased urinary protein to creatinine ratio, excessive casts in urinary sediment, and abnormal renal imaging. It may be a good idea to get the patient used to the idea of certain dietary alterations that will become more necessary if renal function does progressively decline in the future. There is no evidence to suggest that dietary modification (protein or phosphorus restriction) prevents progression of chronic renal disease in either dogs or cats that are not yet azotemic, however.

Dietary protein restriction does reduce GFR, an effect that for BUN is overcome because less urea nitrogen is generated at the same time. It is expected that the BUN will decrease if

adequate calories are taken in at the same time that a high quality and reduced quantity of protein is ingested. The goal is for most of the ingested protein to be used for anabolic processes and not to be degraded to urea and other nitrogenous wastes. Serum creatinine should not change very much, though it may increase to a small degree due to decreases in GFR. Serum phosphorus concentrations should decrease, though not necessarily to the normal range depending on the starting point above baseline. Even though serum phosphorus may decline, the degree of phosphorus restriction in commercially available protein and phosphorus restricted diets may not be sufficient to reverse renal secondary hyperparathyroidism. Dogs and cats in CRF fed diets restricted in protein usually show less proteinuria than those fed higher protein diets. This could simply be a result of the damaged glomeruli already there and the effect of hemodynamic changes following protein feeding. Alternatively, the greater proteinuria observed during high dietary protein feeding could serves as an indicator for further risk of nephron injury. No studies of experimental dogs or cats with severe reduction in renal mass have convincingly shown that dietary protein restriction retarded the progression of CRF. Phosphorus restriction in experimental dogs and cats with CRF does protect against progression of CRF.

There is evidence emerging from studies at the University of Minnesota (Jacob F) that the time interval to uremic crisis is increased in clinical dogs with CRF (serum creatinine fro 2 to 8 mg/dl) that are eating diets that are protein, phosphorus, and sodium restricted as well as enhanced in lipids. Uremic episodes, and mortality were lower in dogs eating the modified vs maintenance diets. Dogs that lived 6 months or longer with their CRF were studied as to the progression of their renal failure on these two diets. Dogs on the modified diet significantly reduced progression of their renal failure (1/S creatinine); this effect was also seen in dogs with serum creatinine less than or equal to 3.0 mg/dl. Dogs with experimental renal mass reduction as the cause of renal failure experienced more weight loss, a greater decrease in rear leg circumference, and more anemia when eating a normal protein diet compared to dogs eating diets with moderate protein restriction over 40 weeks[Polzin 1983]. Over half of the dogs eating the normal protein diet died of uremic complications compared to only 1 of 12 dogs consuming diets that were moderately or severely restricted in protein [Polzin 1984]. Dogs with 75% renal mass reduction did not differ in renal function or degree of histopathology when fed high, moderate, or restricted amount of dietary protein for 4 years[Robertson 1986]. All dogs with 11/12 renal mass reduction had glomerular and interstitial renal lesions at 20 weeks regardless of dietary protein intake. Renal lesions were most severe in those in which GFR increased over time on both protein replete and restricted diets [Polzin 1988]. Dietary restriction of phosphorus and calcium in dogs with severe renal mass reduction resulted in greater survival and increased GFR compared to dogs eating a calcium and phosphorus replete diet (dietary protein not restricted in either group)[Finco 1992]. In another study of dogs with renal mass reduction, dietary phosphorus restriction increased survival and the period of time that GFR was stable, effects that were not seen with dietary protein reduction [Finco 1992].

There are conflicting reports about the effect of dietary protein and calories on the progression of renal failure in experimental cats. Cats with 5/6 renal mass reduction that were fed a protein and calorie restricted diet had lower BUN and GFR compared to cats fed a high protein diet for one year. Cats of this study that were fed the high protein diet ate and weighed more than the cats fed the low protein diet and over half developed hypokalemia while eating the high

protein diet[Adams 1993]. Dietary and caloric restriction resulted in less renal morphologic injury compared to cats eating the high protein diet[Adams 1994]. Another study using cats with experimental renal mass reduction investigated the interactions of high and low dietary protein intake as well as high and low caloric intake for one year. Diets replete in protein were not associated with the development of renal lesions but calorie replete diets were associated with mild non-glomerular lesions [Finco 1998]. A veterinary diet designed for the treatment of renal failure in cats that is both protein and phosphorus restricted was effective in decreasing serum phosphorus and PTH levels in clinical cats with mild CRF [Barber 1999]. In a similar study, feeding clinical cats with CRF a protein and phosphorus restricted diet resulted in decreased BUN, serum phosphorus, and prevented PTH levels from increasing over time. Serum creatinine tended to go down in the restricted diet group of cats and increased in the non-restricted dietary group. Approximately 60% (29/58) of the cats enrolled in this study accepted the diet – protein restricted diets are not palatable to some cats. Cats of this study that were fed the veterinary diet survived a median of 633 days compared to 264 days for cats that ate foods replete in protein and phosphorus[Elliott 2000]. In a third study, clinical cats with CRF that were fed a protein and phosphorus restricted diet (n = 25) decreased serum creatinine from 3.1 to 2.6, decreased serum phosphorus, and gained weight over 24 weeks, while cats on non-restricted diets (n = 10) increased serum creatinine from 3.0 to 3.6, increased serum phosphorus, and lost weight[Harte 1994].

Too much protein restriction can result in malnutrition manifested as weight loss, muscle wasting, lethargy, loss of condition of skin and coat, decreased skin turgor (without dehydration), and decreased resistance of skin to venapuncture. Laboratory evidence for protein malnutrition includes anemia, hypercholesterolemia, and hypoalbuminemia. Acidemia can be exacerbated by too much protein restriction (diminished renal tubular ability to mobilize glutamine to secrete ammonia needed to acidify urine). This combination of clinical and laboratory abnormalities are often attributed to the nature of the advancing renal lesions but should prompt the clinician to ask if they could be caused by protein/calorie malnutrition.

It is controversial as to when in the progression of CRF and to what degree protein restriction should be instituted. Guidelines for protein restricted diets are made to take advantage of their extrarenal benefits. Dietary protein intake can be considered on an absolute basis of Gm/kg/day of protein intake or as the % of calories that are derived from protein (both are important). Dogs develop negative nitrogen balance when the % of protein calories is less than 10% and cats do so when calories derived from protein sources are less than 12%. Both dogs and cats develop decreases in protein reserves when calories from proteins are less than 20%. When the patient does not eat to fulfill its caloric need, the percentage of calories from protein becomes more important. In our scheme, mild protein restriction is provided when proteins provide about 20% of the calories, moderate protein restriction with 15 % of calories from protein, and severe protein restriction when 10% of calories are derived from dietary protein.

Commercial dog foods provide greater than 5 grams/kg/day of protein of varying quality. Normal dogs require a minimum of 1.25 to 1.75 grams/kg/day of high quality protein. The protein requirements for CRF dogs are not known, but they are higher than minimal requirements for normal dogs. Either no or minimal protein restriction is recommended if the serum creatinine

during hydration is less than 2.5 mg/dl. Animals with serum creatinine from 2.5 to 5.0 mg/dl (moderate renal failure) may be managed with 2.5 to 4.0 grams/kg./day of high biologic value protein. More severe renal failure manifested in animals with hydrated serum creatinine greater than 5.0 mg/dl may benefit from 1.5 to 2.5 Gm/kg/day of protein . 2-3 GM/kg/day is provided approximately by 13-17% protein as dry matter. Less is known about protein requirements for CRF cats, but 3.3 to 3.7 grams/kg/day is recommended as moderate protein restriction. It is important that adequate calories are supplied with restricted protein diets, otherwise endogenous and exogenous proteins will be catabolized for energy. The protein and caloric intake must be individualized for each animal. A balance between uremic signs, nutritional status, and desirable serum biochemistry is sought. Protein intake is progressively lowered if severe uremic signs persist. In the face of malnutrition (decreasing body condition score, decreasing lean muscle mass, decreasing serum albumin), protein intake is gradually increased. In general, we try to prescribe the highest level of protein intake that the patient will tolerate during renal failure in order to maintain a good body condition score. A new concept referred to as the "Nitrogen Trap®" involves the feeding of novel fermentable fibers in an attempt to excrete nitrogenous waste products through the colon. Increased colonic blood flow can lead to increased numbers of bacteria in the colon with a subsequent decrease in nitrogenous waste products from the blood as the bacteria use them in their metabolism. This kind of diet potentially allows animals with CRF to eat higher levels of protein without increasing the level of waste products that are generated and maintained.

Phosphorus Restriction

Phosphorus restriction can have beneficial effects on renal histology, renal function, and/or mortality in dogs and cats with chronic renal failure. These effects are independent of protein restriction (ie protein restriction is not necessary to see benefits achieved with phosphorus restriction). It is not precisely known how phosphorus restriction exerts its beneficial effects, but it may be through less renal mineralization and blunted degree of secondary hyperparathyroidism. Less renal mineralization may occur due to lowered concentration and actions of PTH and possibly from a direct lowering of the calcium x phosphorus product.

There are no currently available commercial diets that are both replete in protein and restricted in phosphorus. It is theoretically possible to do so but this process is difficult in commercial formulations. Diets are formulated to be restricted in phosphorus largely by limiting the amount of protein since phosphates are associated with proteins. The dietary source of protein also influences the amount of dietary phsophate . The quantity of calcium and phosphorus supplemental salts as well as the form of the phosphorus supplement influence the degree of phosphorus intestinal absorption. There is considerable variability by veterinary specialty kidney diets in the mg/100 kcal of phosphorus intake that occurs with similar levels of dietary protein restriction. Comparison of specialty veterinary foods by % dry matter and on a mg/100 kcal basis is available at the Nutrition Support Services Web Site of The Ohio State University College of Veterinary Medicine Veterinary Diet Manual Home Page – Diet Tables for Dogs ; Diet Tables for Cats at http://nss.vet.ohio-state.edu/Diet%20Manual/Introtbl.htm. This site was set up and is maintained by Dr. Tony Buffington. Dietary restriction of protein by itself is not sufficient to maintain normal serum phosphorus concentration when GFR is severely reduced. Intestinal phosphorus binders (aluminum hydroxide, calcium carbonate, calcium

acetate) are helpful in these instances. It has been conventional to administer intestinal phosphorus binders only when the serum phosphorus is elevated, but there may be reasons to administer them to CRF animals before elevation in serum phosphorus occurs. Phosphorus intake should be reduced to at least less than 25 % of normal to match the level of reduction in GFR.

Aluminum salts (hydroxide or carbonate) have been used extensively as intestinal phosphorus binders. Chronic toxicity from aluminum has been demonstrated in people with CRF (who are usually on dialysis) manifested in nervous tissue and bone disease. Whether aluminum toxicity is a problem following treatment with aluminum containing compounds in dogs and cats remains to be determined. Calcium carbonate is an alternative to aluminum salt intestinal phosphorus binders. The dose is usually 100 mg/kg divided twice daily with meals. The dose is adjusted after serially evaluating serum phosphorus concentration. Potential problems from aluminum toxicity are avoided, but hypercalcemia can occur especially if simultaneously supplemented with calcitriol. Calcium acetate has been approved for humans as an intestinal phosphorus binder, replacing aluminum salts and calcium carbonate as the phosphorus binder of choice. Calcium acetate has excellent phosphorus binding in the intestinal lumen and less problems with the development of hypercalcemia than encountered with calcium carbonate. Sevelamer HCl (Renagel®) is a non-calcium, non-aluminum containing intestinal phosphate binder that has recently been approved for use in people with renal failure. We have used sevelamer successfully in a small number of dogs and cats as an alternative to aluminum and calcium containing compounds; there are no reports of its efficacy or safety in veterinary medicine to date. Tertiary iron salts are being used as phosphate binders in people in Europe but have yet to be approved for such use in the USA. It should be noted that all intestinal phosphate binders work better when given with food or within a few hours of food ingestion.

Metabolic Acidosis

Metabolic acidosis of varying severity often accompanies chronic renal failure. Anorexia, nausea, vomiting, and weight loss may in part be caused by this acidosis. Muscle weakness, lethargy, hypokalemia, skeletal demineralization, hyperphosphatemia, and hypercalciuria may also exacerbated by chronic metabolic acidosis. Accelerated progression of chronic renal failure attributed to tubular hypermetabolism (ammoniagenesis) during chronic metabolic acidosis has been suggested. Diet influences the degree of acid end-products required for excretion. Egg-protein has traditionally been assumed to be the most biologically-utilizable protein, but studies in dog with chronic renal failure revealed that these diets (high in sulfur-containing amino acids) were acidifying compared to vegetable source protein diets. Lower protein diets can result in less acid for excretion especially if they contain less animal protein sources. Veterinary foods designed for the treatment of renal failure are usually designed to be mildy alkalinizing by the addition of salts that are metabolized to bicarbonate (potassium citrate). Acidifying diets should be discontinued – most grocery store foods in the USA have been formulated to be acidifying in both dogs and cats. Acid-base balance should be re-evaluated after dietary modification to see if supplemental alkali is needed. Sodium bicarbonate, potassium citrate, calcium carbonate, and calcium acetate are sources of alkali.

Potassium Supplementation

Hypokalemia can result in chronic renal failure as reported in cats. Correction of hypokalemia is essential in these instances. Potassium supplementation to cats with chronic renal failure and normal serum potassium concentration is more controversial. A study at OSU failed to show a beneficial effect of potassium gluconate supplementation over that of sodium gluconate in a population of cats with chronic renal failure and normal serum potassium. Veterinary foods designed for renal failure often contain additional potassium supplementation in the form of potassium citrate.

Dietary Lipids

Intrarenal vasoconstriction or vasodilatation occurs in response to eicosanoids derived from dietary fatty acid intake. It appears to be possible to select specific dietary lipids to enhance or decrease vasoconstriction. Recent studies in experimental dogs demonstrated that certain dietary lipids exerted a protective effect on renal function and histology whereas other dietary lipids exacerbated progression of CRF. If such effects are demonstrated in clinical animals with CRF, modification of dietary lipid intake could prove useful to prolong the life of severely damaged kidneys. Dogs with 15/16 renal mass reduction were studied for 20 months while eating basal foods supplemented with lipid to achieve a 15% concentration. Dogs treated with omega-3 PUFA supplementation (menhaden fish oil) developed fewer renal lesions (expansion of mesangial matrix, glomerular sclerosis, and interstitial inflammation) compared to those in dogs receiving either omega-6 PUFA (safflower oil) or saturated fatty acids (beef tallow). Lower levels of proteinuria, serum creatinine, cholesterol, and triglycerides were found in dogs that received omega-3 supplentation. Global GFR was greater in dogs treated with omega-3 PUFA compared to omega-6 PUFA [Brown 1998]. Intraglomerular hypertension and hypertrophy were observed in dogs treated with omega-6PUFA. Clearly, supplementation with omega-3 was renoprotective, while supplementation enhanced renal injury under the conditions of this study. The amount of additional dietary lipid provided in this study in order to see these effects was substantial. Dogs of this study had very severe reduction in renal mass – whether similar effects would be seen in dogs with less severe loss of renal mass is unknown. How important is the absolute dose of omega-6 or omega-3 versus the ratio of omega 6 to omega 3 ? Single nephron micropuncture studies in dogs show that a ratio of omega-6 to omega-3 of 5:1 was "protective" in that glomerular capillary pressure increased very little. Much larger increases in glomerular capillary pressure are observed at dietary ratios of 25:1 and 50:1.

Sodium Intake

Most diets designed for use in CRF are limited in sodium content on the basis that this may help to treat systemic hypertension that may be common in both dogs and cats with chronic renal failure. Sodium restriction alone however is not sufficient to treat hypertension associated with chronic renal failure in dogs or cats. Gradual conversion to sodium-restricted diets is recommended as the CRF kidney has adapted to provide natriuresis per remaining nephron. A sudden decrease in dietary sodium intake could result in dehydration as it may take time to decrease the natriuretic response.

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CALCITRIOL IN TREATMENT OF RENAL HYPERPARATHYROIDISM

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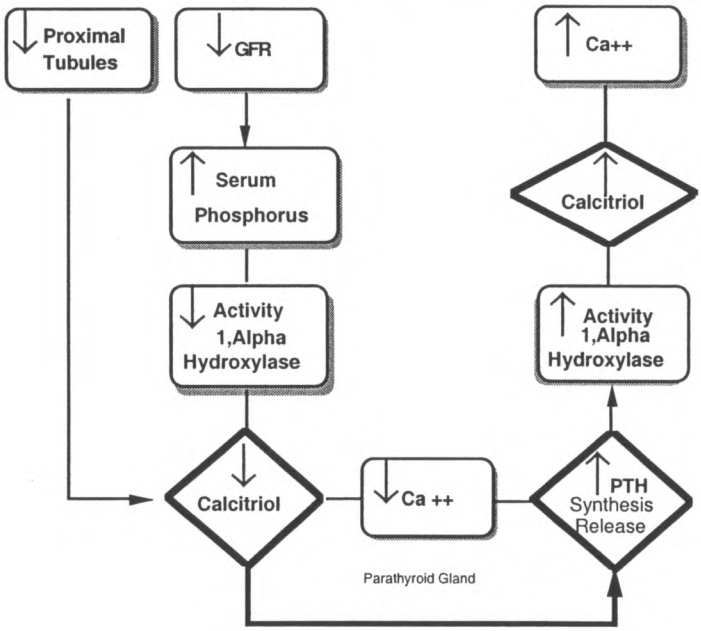
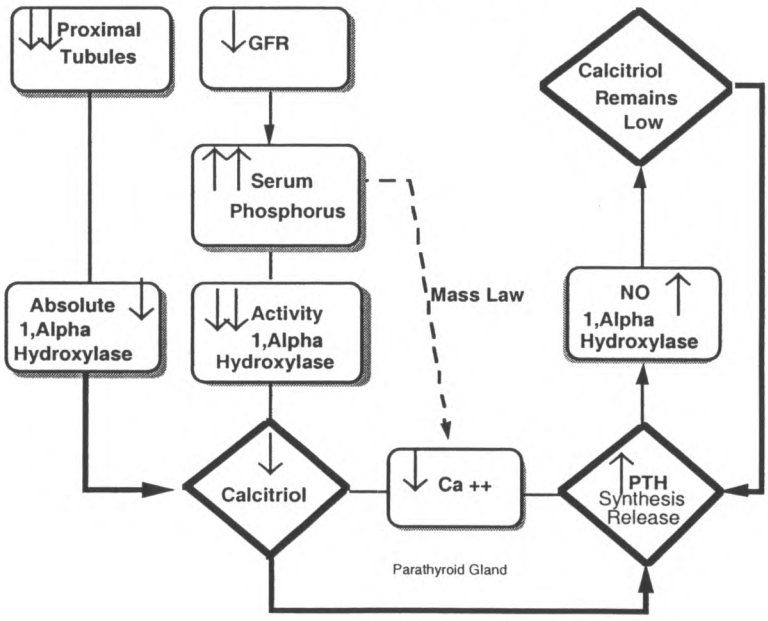
Pathophysiology - Development of Renal Secondary Hyperparathyroidism

Fig 1a. Calcitriol "Trade-Off" Hypothesis
EARLY CHRONIC RENAL FAILURE



Major Mechanism of Action

Fig 1b. Calcitriol "Trade-Off" Hypothesis
LATE CHRONIC RENAL FAILURE



Major Mechanism of Action

Figure 1a and 1b emphasize the importance of either relative or absolute calcitriol deficits in the evolution of renal secondary hyperparathyroidism. Increased serum phosphorus decreases serum ionized calcium to a substantial degree by mass-law effect only when the increases in serum phosphorus are very large. The finding of a normal calcitriol concentration has often been erroneously interpreted to mean that calcitriol deficits do not occur or are not important early in chronic renal disease. Normal serum calcitriol and calcium concentrations in these instances, however, are established and maintained by the "correcting forces" of increased levels of parathyroid hormone (PTH). In more advanced stages of renal disease, absolute decreases in calcitriol and calcium concentrations do occur. Renal secondary hyperparathyroidism is the result of increased secretion of PTH by each cell as well as increased number of cells due to hyperplasia. Within the parathyroid gland nucleus, adequate concentrations of calcitriol are necessary to inhibit genomic transcription for PTH synthesis as well as to exert antiproliferative effects to maintain normal cell numbers. Adequate concentration of intracellular ionized calcium is necessary to allow calcitriol to exert its "silencing" effect on PTH transcription.

Clinical Signs Caused by Excess PTH and/or Deficits of Calcitriol

PTH is a major uremic toxin. The toxic effects of PTH on tissues are best-known on bone (fibrous osteodystrophy, "rubber-jaw"), but many tissues are adversely effected by high levels of circulating PTH. Initially, increased levels of PTH are adaptive for the control of divalent ion metabolism (calcium, phosphorus). It appears that increased PTH levels become maladaptive when concentrations increase beyond a threshold of 3 to 5 times baseline. Above 5 times baseline for intact PTH, severe bone disease occurs and the thresholds for injury to other tissues , although somewhat variable, seem likely to be in this range. The dominant change in tissues adversely affected by excess PTH is that of increased cytosolic calcium concentration to toxic levels. Tissues with the highest concentrations of the PTH/PTHrP receptor will be those affected earliest and most severely. Some of the toxicity usually attributed to increased PTH may in certain instances be directly due to a lack of adequate calcitriol, as there are calcitriol receptors in most tissues. PTH levels referred to are those measured by a validated assay which measures intact-PTH. In uremic cats, it may be necessary to dilute the serum prior to analysis in order to remove interference from carboxy-terminus PTH molecules when using an intact PTH immunoradiometric method.

Central nervous system depression and detrimental effects on the peripheral nerves are common in chronic renal failure, caused in large part by excess PTH. Part of the anemia of CRF may be caused by PTH excess. Abnormal lipid and carbohydrate metabolism can also be caused by excess PTH and could contribute to the anorexia of uremia. Weakness from skeletal muscle myopathy during uremia may be caused by both excess PTH and lack of calcitriol receptor activity within muscle cells. Some of the reduced physical activity of uremic dogs and cats may be attributed to bone changes of excess PTH, although this is difficult to separate from the other effects of uremia. Obvious bone pain in animals is rare despite the universal presence of histologic bone lesions in chronic renal failure - bone is the earliest tissue to exhibit histologic evidence of hyperparathyroidism perhaps due to its high concentration of PTH receptors. Increased renal cellular calcium content caused by increased PTH is toxic and has a role in the

relentless progression of chronic renal disease. Renal tubular cells have high concentrations of the PTH receptor and are among the body tissues affected earliest by excess PTH.

Control of Renal Secondary Hyperparathyroidism :
Diet, Intestinal Phosphorus Binders, and Calcitriol

Dietary phosphorus restriction as single modality treatment is capable of lowering PTH levels in some dogs and cats with chronic renal disease or early renal failure (Figure 2). Those with greater loss of renal function will require addition of a phosphorus binder given with the food to enable enough phosphorus restriction proportionate to the loss of renal mass. Return of serum phosphorus to normal does not guarantee that PTH levels will return to normal, as phosphorus restriction only works in those that have enough active tubular machinery capable of calcitriol synthesis once the inhibitory effects of excess phosphorus on calcitriol synthesis are removed.

Effectiveness of Low Daily Doses of Calcitriol in Reduction of Renal Secondary Hyperparathyroidism in Dogs and Cats

Supplementation with calcitriol to dogs and cats with CRF is designed as a daily therapy for life. Low daily oral doses of calcitriol effectively return PTH levels to either normal or below the toxic threshold. This effect may take months before the full effect is seen when a dose of 2.5 to 3.5 nanograms/kg once daily is prescribed. Dogs with experimental subtotal nephrectomy required 6 nanograms/kg to effectively lower PTH levels at one month, a dose that we infrequently prescribe for those with refractory cases of hyperparathyroidism.

Adequate control of serum phosphorus to concentrations less than 6.0 mg/dl is essential prior to and during prescription of calcitriol treatments. Phosphorus restriction relieves phosphate-mediated inhibition of the renal 1-hydroxylase system resulting in enhanced endogenous synthesis of calcitriol and subsequent inhibition of PTH synthesis (Figure 1). A second reason to institute phosphorus restriction is to reduce the likelihood of soft-tissue mineralization by reducing the serum calcium-x-phosphorus product. A third reason is to increase ionized calcium concentrations that are operative in the parathyroid gland nucleus. Calcium with its associated transcription factor must bind to its DNA binding site in the parathyroid cell nucleus in order to fully allow the silencing effect of calcitriol to decrease the synthesis of PTH. As serum phosphorus is reduced, calcium ionization increases. Serum phosphorus in excess of 7 or 8 mg/dl provides enough mass-law effect to decrease ionized calcium about 0.1 mg/dl, enough to increase PTH secretion. It is almost certain that control of secondary hyperparathyroidism will fail in patients who maintain serum phosphorus much above the normal range. The effectiveness of calcitriol in control of hyperparathyroidism has been noted to increase in patients in whom serum phosphate was lowered.

Hypercalcemia is a very uncommon side-effect of low-dose oral calcitriol treatment in our experience. When noted, it is usually associated with the use of calcium-containing intestinal phosphate binders, especially calcium carbonate. Hypercalcemia can be minimized by giving calcitriol at nighttime on an empty stomach if necessary. When evaluated in parallel with calcitriol, so-called non-calcemic calcitriol analogues were calcemic at effective doses and showed no advantage over calcitriol which remains the gold-standard agent. 1-alpha-

hydroxycholecalciferol (available in Europe, Leo Pharmaceutical), a calcitriol precursor, is as effective as calcitriol in doses about 1.5 times that of calcitriol.

Though PTH levels decline following calcitriol treatments, it is inherently difficult to objectively prove the clinical benefits of lowering PTH levels in dogs and cats with renal disease or failure. Parathyroidectomized dogs with experimental subtotal nephrectomy had more stable levels of renal function during the second year of study than did dogs without reduction of PTH. Calcitriol therapy appears to exert an overall improvement in brain wave function of uremic dogs in a preliminary study in our hospital. Hundreds of veterinarians that have been prescribing calcitriol as treatment for their uremic dogs and cats responded to a recent survey from one of us(LAN). The vast majority either strongly agreed or agreed with the following statements for both dogs and cats : 1. Patients seem brighter, and more alert, and interactive with owners. 2. Patients seem to have an improvement in appetite. 3. Patients seem to be more physically active than previously. 4. Calcitriol treated patients seem to have longer lifespans. Veterinarians of this survey were selected on the basis that they have prescribed calcitriol in at least 5 patients in order to get their opinion. Results of this subjective survey provide impetus to further study the effects of calcitriol in dogs and cats with naturally-occurring renal disease and renal failure.

SIMPLIFIED SYNOPSIS

PTH levels often decline following oral low-dose calcitriol treatments in dogs and cats with renal failure. Does this reduction in PTH level improve survival time, quality of life, level of GFR and/or degree of renal lesions? Double-blind placebo-controlled studies of calcitriol treatment in clinical dogs or cats with renal failure have not been performed to enable these questions to be adequately answered. Clients and veterinarians often comment that calcitriol seems to result in overall improvement of well-being in renal failure animals compared to those of similar degree renal failure that do not receive calcitriol.

Increased survival times of calcitriol treated renal failure dogs and cats are suspected, but survival times of dogs or cats with untreated or non-calcitriol treated renal failure animals is lacking. Clinical cats with CRF and adequate control of PTH (dietary protein and phosphrous restriction) lived about three times longer than cats with uncontrolled hyperparathyroidism (Elliott and Barber). Parathyroidectomized dogs with experimental renal failure had more stable and higher levels of GFR during the second year of study than did renal failure dogs without reduction of PTH. Seven of eight dogs with PTH reduction lived for the second year while only 3 of eight dogs with sham PTH surgery survived the same time period. Additionally, less severe mesangial matrix changes and soft tissue mineralization as well as more preserved bone mineralization were noted in the dogs with PTH reduction (Finco AJVR 1997). Calcitriol therapy exerted an overall improvement in brain wave function of uremic dogs in a preliminary study in our hospital. A controlled prospective study of dogs with CRF treated with calcitriol is underway at the University of Minnesota (Polzin 2000).

Calcitriol Protocol for Dogs and Cats with Chronic Renal Failure

1. Start standardized dose of 2.5 ng/kg SID for routine cases – check calcium at 1 and 3 weeks.

2. A convenient method to provide calcitriol to small animals is to take one 0.5 microgram capsule of calcitriol (Roche Pharmaceuticals) and dilute it in 20 ml light olive oil. Each 0.1 ml

then contains 2.5 ng calcitriol. Most cats are dosed with 0.3 to 0.4 ml once daily. It is important to keep the calcitriol olive oil solution in a dark container to keep light from destroying the calcitriol. We support this method for providing calcitriol as long as it is not stored for appreciable periods (a month supply at a time is suggested to be stable).

3. Alternatively, compounding pharmacies will provide capsules with a prescribed ng content and stabilizing agents. They will also provide various concentrations of calcitriol in pharmaceutical oil. With stabilizing agents, the preparation is stable for many years.

4. 1-alpha-hydroxy-cholecalciferol (Leo Pharmaceuticals, Denmark) is available as a calcitriol precursor converted in the liver by 25-hydroxylation to calcitriol. The doses of 1-alpha-hydroxy-cholecalciferol need to be increased compared to calcitriol by about 50% since not all precursor is converted to calcitriol.

5. For those with 10 x increase or greater in PTH, consider pulse therapy first. Consider pulse therapy for those who fail to adequately suppress PTH on standard low dose calcitriol.

6. Give 20 ng/kg twice weekly for one month and recheck PTH. Make sure to give the high doses of calcitriol at night before the animal's bedtime on an empty stomach to minimize calcium absorption from the intestine.

7. Pulse dosing is an attempt to treat "nodular" hyperplasia of the PTG that occurs from single clones of PTG cells with very few calcitriol receptors. The hope is to induce more calcitriol receptors so that calcitriol will then be able to exert its negative effect on PTH synthesis.

8. If PTH still elevated substantially at one month recheck, increase dose to 25 ng/kg twice weekly for the next month and recheck PTH levels. Increase dose by 5 ng/kg each month if PTH levels do not decline.

9. Check calcium levels at 1 and 2 days after the 3rd dose to make sure that bothersome hypercalcemia is not developing. It is conceivable that some hypercalcemia can occur rapidly as a result of transcaltachia, a direct cell membrane effect on the intestinal epithelium independent of any genomic effects that calcitriol exerts later.

10. When PTH levels have returned to normal or near normal, start daily low dose calcitriol therapy.

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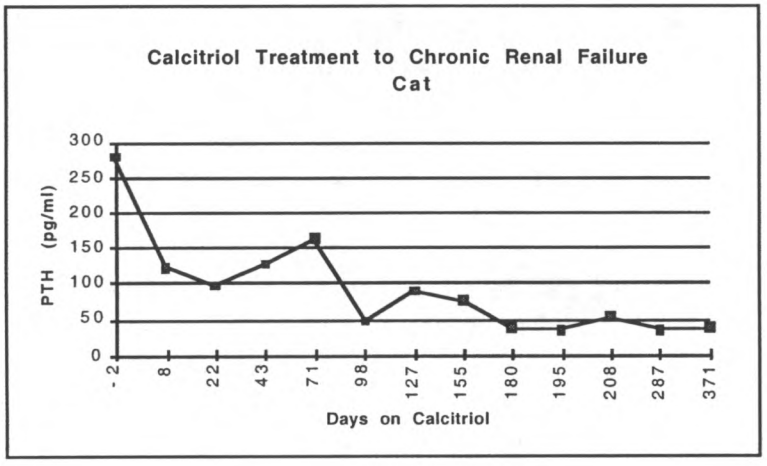
Fig 2.



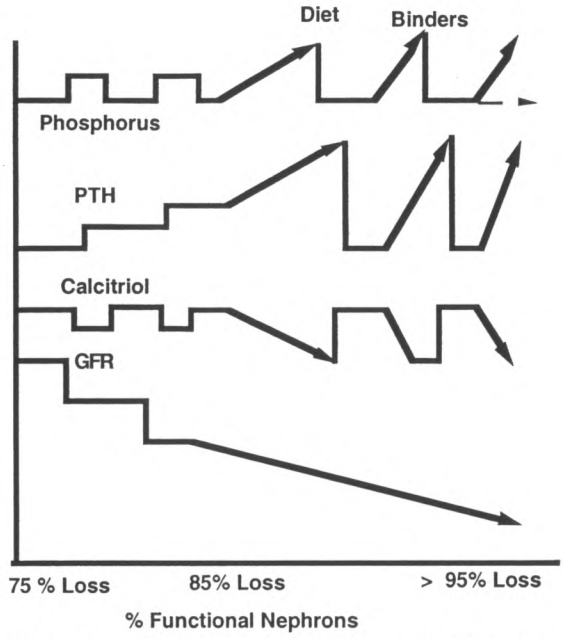


Fig. 3) The initial portion of this figure illustrates the typical abnormalities of untreated progressive chronic renal failure (loss of nephron mass). Dietary restriction of phosphorus initially results in correction or reduction of hyperparathyroidism (HPTH), but only temporarily as further GFR is lost. The addition of phosphate binders to the phosphate restricted diet results in reduced PTH concentrations, but PTH becomes increased again if sufficient nephrons continue to be lost. HPTH eventually develops with extensive loss of nephron mass even when serum phosphorus remains normal with the use of dietary restriction and phosphate binders (dashed arrow top right).

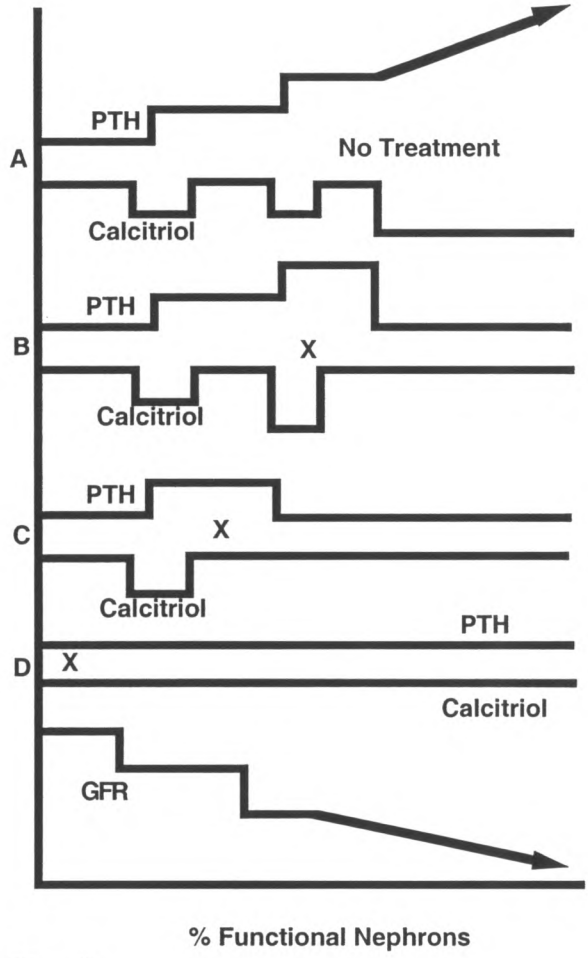


Fig. 4)
A = No calcitriol supplementation. Calcitriol normalizes only at the expense of elevated PTH.

B = Calcitriol treatment is started at time "x" late enough in the renal disease when calcitriol is decreased and PTH is elevated with restoration of both to normal.

C = Calcitriol treatment is started at an early enough stage where calcitriol concentrations are still normal as a consequence of the increased PTH. Calcitriol supplementation remains beneficial to maintain normal calcitriol concentrations while decreasing PTH.

D = Calcitriol treatment is started very early in the course of progressive nephron loss, prior to either PTH increase or calcitriol decrease.

Role of ACE-Inhibition in Renal Disease

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Angiotensin-II plays a pathophysiologic role in proteinuria and the progression of renal disease. It may play a role in the progression of non-proteinuric renal diseases too. Angiontensin-II receptors exist within glomeruli and vasculature of the renal tubules[Yamada 1990]. Converting enzyme facilitates the generation of angiotensin-II from angiotensin-I either locally within the kidney via brush border of proximal tubules or via activity of systemic endothelium. Angiotensin-II activity within the kidney causes vasoconstriction of glomerular arterioles with a preferential effect exerted at the efferent arteriole compared to the afferent arteriole. Vasoconstriction of the efferent arteriole at a time of no change in the afferent arteriole increases intraglomerular capillary pressure. Progression of renal disease in remnant nephrons can be attributed in part to the persistence of intraglomerular hypertension, a process that is associated with increased trafficking of marcomolecules into the mesangium with resulting proliferation of mesangial cells and increase mesangial matrix (glomerulosclerosis). Angiotensin-II has non-hemodynamic effects that are potentially important since it can act as a growth factor and stimulate other growth factors that influence renal vascular and tubular growth.

The use of ACE-I decreases systemic blood pressure as well as the degree of intraglomerular hypertension, and may prevent loss of heparin sulfate that can occur in glomerular disease thereby limiting the degree of proteinuria. ACE-I may limit renal growth in chronic renal disease, as well as decrease the size of the endothelial pores within glomeruli again limiting the degree of proteinuria[Grauer 2000]. The magnitude of proteinuria has been shown to be a good predictor of progression of CRD in people and rats[Gruaer 2000; Klahr 1999; Ots 2000]. Excess proteinuria can damage renal tubules which then synthesize excess vasoactive and inflammatory substances that favor infiltration of interstital inflammatory cells and renal scarring[Zoja 2000]. Decreased infiltration of macrophages and dowregulation of proinflammatory cytokines are also possible renoprotective effects following ACE-I [Ots 2000].

There is growing evidence that angiotensin-converting enzyme inhibitors (ACE-I) reduce systemic blood pressure, reduce proteinuria, and slow the progression of a variety of renal diseases in humans [Maschio 1996; Kshirsagar 2000] and dogs[Grauer 2000]. The best response appears to be seen in people with glomerular disease and substantial proteinuria and in the prevention of the progression of diabetic nephropathy. Substantial benefit has also been achieved in people with non-diabetic progressive nephropathies. Lisinopril treatment of dogs with experimentally induced diabetes mellitus and reduction in renal mass resulted in reduced glomerular transcapillary pressure, hypertrophy of glomerular cells, proteinuria, and mean arterial pressure[Brown SA, 1993].

There is one clinical study in dogs[Grauer 2000] regarding the use of ACE inhibition for the treatment of renal disease. Samoyed dogs with x-linked hereditary nephritis undergoing treatment with enalapril experienced less proteinuria, increased excretory function, less glomerular basement membrane splitting, and greater survival times than control dogs[Grodecki

1997]. Twenty-nine clinical dogs with glomerular disease (16 membranous GN and 13 membranoproliferative GN) were treated with either enalapril at 0.5 mg/kg once or twice daily (n = 16) or placebo (n = 14) as a means of ACE inhibition for 6 months in a multi-center prospective double-blind study stratified within glomerular disease diagnosis. Doses of enalapril or placebo were increased from once to twice daily if < 50% reduction of UPCR was achieved following one month of treatment. One dog received both placebo and enalapril. All dogs also were concurrently treated with aspirin at 0.5 to 5.0 mg/kg once or twice daily as well as with a moderately protein-restricted diet designed for the treatment of renal failure dogs. Enalapril and placebo groups were equally matched at the start with regard to degree of azotemia, systolic blood pressure, and glomerular histologic score but the dogs receiving enalapril had greater UPCR (8.7±4.4 vs 4.7±2.3) than control dogs.

There were significant differences between groups after 6 moths of treatment for UPCR (-4.2±1.4 vs 1.9±0.9), and UPCR x serum creatinine(-6.3±10.5 vs 8.3±10.1), systolic blood pressure (-16.7±7.0 vs 6.8±6.8 mm Hg), and response scores (1.4 ±0.8 vs 0.3±0.5) for enalapril vs control dogs respectively. Response scores were assigned as 0, 1, or 2 based on magnitude of change in UPCR and serum creatinine (higher scores were more stable or improving). Serum creatinine was 1.6±0.6 initially and 2.7±1.5 at 6 months in the placebo treated dogs compared to 1.9±0.6 and 1.7±0.7 in the enalapril treated dogs.

In the enalapril group of dogs, 9 improved, 4 had no progression and 3 showed progression; euthanasia due to renal failure occurred in two dogs at 3 and 5 months of the study. Enalapril was given once daily in 7 dogs throughout, twice daily in 6 dogs starting at one month, and twice daily in 3 dogs starting at 3 months. Most dogs that showed decreased UPCR (7/9) had the most marked decreases by the one-month evaluation with minimal further decreases thereafter. No dogs treated with placebo improved, 4 showed no progression, and 10 showed progression. Placebo was given once daily in 3 dogs, twice daily in 9 dogs starting at one month and twice daily in 2 dogs starting at 3 months. In the one dog in which placebo treatment was followed by enalapril, no progression occurred during placebo treatment and then improvement occurred while on enalapril. Improvement in this study was defined as greater than or equal to a 50% decrease in UPCR with stable serum creatinine, no progression was defined as < 50% decrease in UPCR with a stable serum creatinine, and progression was defined as > 50% increase in UPCR and or serum creatinine.

Enalapril treatment of clinical dogs with idiopathic glomerulonephritis reduces proteinuria as well as systolic blood pressure and delays the onset of azotemia that would otherwise occur at least for six months[Grauer 2000]. Similar benefits on proteinuria and delayed onset of azotemia were seen in Samoyed dogs with hereditary nephritis treated with enalapril but without decreased systolic blood pressure[Grodecki 1997]. No correlation between change in systolic blood pressure and change in UPCR could be established in either enalapril or placebo treated clinical dogs[Grauer 2000].

Questions remaining to be anwered : Will the renoprotective effect of enalapril treatment of dogs with more severe azotemia than encountered in the Grauer study (serum creatinine < 3.0) be effective? Will enalapril have the same effect in dogs with renal disease that do not have UPCR > 3.0 (those with minimal or absent proteinuria) ? Will the renoprotective effects of

enalapril in dogs with glomerulonephritis last longer than the 6 month period that has been studied so far ? Will enalapril treatment of dogs with renal amyloidosis have any salutary effect ?

Will enalapril exert similar beneficial effects in cats with advancing renal disease ? Enalapril has not been studied in cats to date but benazepril has recently undergone extensive study as treatment for 201 European cats with CRF due to a variety of causes (not just proteinuric ones). Cats of this study either received benazepril (0.5 to 1.0 mg/kg once daily [Fortekor®]; mean dose 0.73 mg/kg) or placebo. The BENRIC (Benazepril in Renal Insufficiency in Cats) Study Group utilized a number of practices to enroll cats with CRF. Beneficial effects over placebo were seen for quality of life, improvement in appetite, weight gain, and extended life expectancy. Quality of life also increased in the placebo group (restricted protein and phosphorus diet). Minor weight gain occurred in the placebo group; more impressive weight gain was observed in cats over a 12 month period that received benazepril especially those cats that had more severe CRF. Average survial of benazepril treated cats was 501 days vs 391 days for plaebo treated cats. When cats with severe CRF were considered, survival was 401 days in benazepril treated cats vs 126 days for control cats.

Should enalapril or other ACE-inhibitors be given to dogs or cats with any renal disease likely to progress ? My suspicion is yes. Proof is available only for dogs with the protein-losing nephropathy of idiopathic glomerulonephritis. If enalapril or benazepril is chosen for treatment, the dog or cat should return to the clinic to repeat serum creatinine measurement in one to two weeks. This is to make sure that GFR has not been reduced too much as a consequence of efferent arteriolar dilatation during therapy; repeat systemic blood pressure determination should also be undertaken at this visit to ensure that systemic hypotension is not developing. Remember that "super nephrons" as compensation for CRF become so by increasing single nephron GFR mostly by afferent arteriolar dilatation and that efferent arteriolar dilatation from ACE-I may dramatically decrease this single nephron GFR. Any detected decrease in GFR and rise in serum creatinine is usually transient and reversible following discontinuation of the drug. It is important to note that development of azotemia is not dependent on the presence of systemic hypotension as the effect of ACE-I can occur earlier within the glomeruli to create intraglomerular hypotension. Hopefully, if systemic hypotension is present and detected early enough, the worsening of azotemia will rapidly return to previous baseline levels following IV fluids. Uncommonly, the development of systemic hypotension in those with chronic renal failure can add an element of "acute-on-chronic" renal failure that will not immediately abate due to acquired renal ischemia and tubular necrosis. Repeat analysis of UPCR is recommended after one month of treatment. If the UPCR has not decreased appropriately, the dose of enalapril is usually doubled.

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Erythropoietin Therapy for Anemia in Chronic Renal Failure : Risks and Benefits

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Anemia is common in dogs and cats with CRF; its severity is correlated with the degree of azotemia in dogs[King, 1992]. Severe anemia is generally encountered in those patients with the most advanced renal disease (highest serum creatinine concentration), though exceptions do occur. This anemia is usually characterized as a non-regenerative, normocytic and normochromic and was described in 12 of 17 dogs with CRF in one study[King, 1992]. Another description is that of hypoproliferative anemia which describes inadequate red cell production by the bone marrow secondary to either an absolute or relative deficiency of erythropoietin needed to stimulate the marrow. Erythropoietin is synthesized within normal kidneys by interstitial cells of the renal cortex [Randolph, 1999], but diseased kidneys lose their ability to adequately manufacture it. Erythropoietin is synthesized in sufficient quantities by normal kidneys to maintain normal red blood cell mass but erythropoietin concentrations are either "normal" or low in dogs[King, 1992; Pechereau, 1997] and cats[Pechereau, 1997] with chronic renal failure ; normal range values of erythropoietin are inappropriately low for an animal with anemia (relative vs absolute deficit). The availability of laboratories to measure erythropoietin is limited; it is not customary nor necessary to measure erythropoietin levels in patients with obvious CRF as the source of the anemia. Though the primary cause of anemia in CRF is related to deficits of erythropoietin, reduced red blood cell life-span (hemolysis), blood loss (GI ulcers, reduced platelet function), and suppression of marrow response by uremic compounds including PTH may contribute at times. Iron deficiency and malnutrition can also decrease the erthropoietic response.

The anemia of CRF contributes to anorexia, weight loss, weakness, lethargy, depression, and behavioral changes since many of these signs are ameliorated if the anemia is corrected [Cowgill, 1998]. Often the clinical signs in CRF are attributed to that of "uremia" though many of them may at least in part be created by anemia. The benefit of correcting even mild anemia is apparent subjectively in some animals (the "feel good" factors and improvement in appetite and

strength). We often underestimate the effects of mild anemia, though it is known from experiences in human medicine that effects of mild anemia can be profound in their patients.

Some increase in hematocrit (PCV %) can occur if the magnitude of azotemia is reduced through adequate dietary protein restriction; too severe a protein restriction may worsen the anemia. Anabolic steroids such as oxymetholone and stanozolol may have some beneficial effect to stimulate the bone marrow, but the effect appears to be weak (if it exists at all) and it may take many weeks to observe the effect. Deca-Durabolin (nandrolone decanoate) at 1 to 5 mg/kg IM once weekly has been recommended by veterinary nephrologists, but convincing reports of efficacy are lacking. Blood transfusions may be necessary. If the PCV is less than 20%, transfusion is likely to benefit the patient. If red cells are needed now, blood transfusion is needed since an effective response to EPO takes weeks. Conventional wisdom considers transfusion as unnecessary when the PCV is in excess of 20 to 25 %. Some uremic animals that are minimally anemic achieve a boost following transfusion that allows them to feel better and eat more food. Increased serum phosphorus and metabolic acidosis result in increased ability to carry and deliver oxygen with lower number of red blood cells. Transfused red cells do not last as long in the uremic plasma as they would otherwise. Multiple transfusions can result in transfusion reactions and shortened red blood cell life-span. Hemolysis and hemoglobinuria may add further injury to an already chronically injured kidney.

Human recombinant erythropoietin (r-HuEPO; EPO®- Amgen) has successfully been used for the treatment of anemia in some uremic dogs and cats, however it is not approved for use in either species. Correction of anemia is achieved within one month of uninterrupted treatment with r-HuEPO in uremic dogs and cats [Cowgill, 1998]; reticulocytosis accompanies the increase in red cell mass. Unfortunately, many dogs and cats with CRF develop a clinically relevant level of antibodies against the human form of erythropoietin following treatment with r-HuEPO. There is an 18.7% difference in primary amino acid sequence between r-HuEPO and r-CaEPO [MacLeod, 1998] which can render r-HuEPO immunogenic in non-target species. Progressive anemia developed during r-HuEPO treatment in 2 of 3 dogs treated more than 90 days (detected at 51 and 80 days) and in 5 of 7 cats treated longer than 180 days (detected

between 37 and 160 days in 4 cats and somewhere between day 150 and 302 in the fifth cat). Anti–r-HuEPO antibodies were detected at time of anemia and persisted for longer than 6 months in some instances [Cowgill, 1998]. Anti-r-HuEPO antibodies were detected at the time anemia developed in 7 of 32 normal dogs give r-HuEPO for twelve weeks[Cowgill, 1994]. Six of 6 normal experimental Beagles that received r-HuEPO by subcutaneous injection in another study developed non-regenerative anemia within 16 weeks, with 4 of 6 doing so by 4 weeks of treatment. Recovery from anemia occurred in all dogs over 5 to 11 weeks (7 week median)[Randolph, 1999]. Interestingly in another study, anti-r-HuEPO antibodies only developed in normal Beagles when treated with r-HuEPO IV at 3,000 U/kg/da; IV doses of 100 or 500 U/kg/day for 3 months did not result in detectable levels of antibodies [Bader, 1992 #57]. Increased red cell mass was maintained in 2 CRF cats treated with 50-100U/kg r-HuEPO IV either once weekly or every other week as needed for 25 to 85 weeks without recurrence of anemia [Suda, 1993 #46].

Anti-EPO antibodies may cross react with what little endogenous erythropoietin is produced within the body as well as that administered exogenously, actually making an anemia worse than before treatment with EPO was started. In these instances, r-HuEPO is initially effective in maintaining the HCT within the target range, but progressively loses effectiveness despite increased EPO dose. Due to the frequency of development of anti-EPO antibodies and their protracted adverse effects on red blood cell production, human recombinant EPO cannot be recommended for use in uremic dogs or cats unless they are already transfusion dependent. There is no commercially available blood test to measure for the development of anti-EPO antibodies. An increase in M/E ratio in bone marrow cytology occurs prior to an obvious decrease in PCV. Uncommon adverse effects associated with r-HuEPO treatment included transient and reversible polycythemia, pain at the injection site, hypersensitivity–like cutaneous or mucocutaenous reactions, systemic hypertension (normal or low PCV), and seizures (in association with moderate to severe azotemia) ; vomiting and uveitis were observed sporadically and only in cats. Polycythemia in normal dogs treated with r-CaEPO developed more readily than in dogs treated with r-HuEPO suggesting a more powerful receptor effect for homologous EPO [Randolph, 1999] – lower doses may be effective when using species-specific EPO.

Treatment with human recombinant EPO can result in a maximal 1 % per day increase in HCT over the first month. When indicated (transfusion dependency), the dose is often started at 100 Units/kg subcutaneously three times per week until the target hematocrit (Dogs = 37-45 % ; Cats = 30-40 %) is reached, usually within 3 to 4 weeks. If the target HCT is not reached by this time, increase the EPO dose by 25 to 50 Units/kg for each injection. If the target HCT is still not reached by 8 to 12 weeks, look for other problems (iron deficiency, blood loss, hemolytic disease, concurrent infections, inflammatory disease, or neoplastic processes). The unusual combination of reticulocytosis (large cells) and tendency for overall microcytosis (decreasing MCV) has been noted during r-EPO treatment of CRF dogs and cats by two veterinary investigors [Cowgill, 1998; Randolph, 1999]

Three of 6 dogs and 3 of 7 cats had iron concentrations less than the reference range in one study of uremic patients. Despite this, resistance to the effects of r-HuEPO that could be attributed to iron deficency was not observed[Cowgill, 1998]. The need for iron increases markedly during erythropoiesis so it is recommended to provide supplemental iron during EPO treatments to maximize the erythopoietic response. Ferrous sulfate at 10 mg/kg PO once daily or every other day has been recommended at the start of EPO treatments, but this dose may be too low based on assessment of iron stores in experimental dogs treated with r-CaEPO [Randolph, 1999]. Oral iron treatments may not be tolerated well by cats [Cowgill, 1998].

What should you do if a decision to treat a dog or cat with human recombinant EPO has been implemented and you suspect that anti-EPO antibody production has become a problem? In these instances an initial salutary response to EPO (increased PCV) occurs but is followed by progressive decline in PCV. If no other problem that could interfere with red cell formation or cause blood loss is found, stop EPO treatments and support with transfusions as needed until the anti-EPO antibodies are cleared. Unfortunately, animals may require intermittent blood transfusion for several months until the anti-EPO antibodies have been cleared.

Erythropoietin that is specific for the dog or cat protein is not presently commercially manufactured. Researchers at Cornell University (MacLeod JN) have cloned the gene for canine specific erythropoeitin (r-CaEPO) and have reported its safety in normal dogs. A study is underway at Cornell to determine the effectiveness of canine recombinant erythropoietin in the treatment of the anemia of chronic renal failure in dogs, including those have failed treatment with human recombinant erythropoietin. Studies using recombinant feline EPO are now underway by the same group. Perhaps some drug company will take it upon themselves to prepare species-specific forms of erythropoietin that will effectively treat the anemia of chronic renal failure without development of anti-EPO antibodies. In the meantime, is there some way that we could modify the way that we use human recombinant EPO so it would be safe and effective? Would less frequent exposure to the human recombinant EPO elicit less of an immune response from the uremic dog or cat? Is IV administration less immunogenic than the subcutaneous route? Would lower doses result in less activation of the immune system? Can the human recombinant form of EPO be given less frequently so as to get a boost of red cell production intermittently without increasing the risk for anti-EPO antibody formation? These are all interesting questions posed to me by practitioners - answers to which I do not know.

A novel form of gene therapy is under consideration in which the canine or feline gene for erythropoietin is inserted into a vector virus and then injected into the animal's muscle. As the genetic material for erythropoietin is taken into the muscle cell DNA, dog or cat specific erythropoietin would be synthesized and secreted by the muscle cells. A dose-related increase of hematocrit was seen in normal cats following IM injection of adeno-associated vector virus laden with the feline EPO gene for the seven weeks of the study [Beall, 2000]. Dose related erythropoietic effects were seen in the bone marrow and spleen of these EPO-gene treated cats. Serum EPO levels increased following EPO gene injection but not always in direct proportion to the number of gene particles given. An Fe-EPO gene treatment study of cats with CRF and anemia started in late 1999 at The OSU Veterinary Medical Teaching Hospital. Two of 5 CRF cats treated in this study developed polycythemia; one is alive and requires periodic phlebotomy and one died shortly after the development of polycythemia (cause and effect could not be definitively established). Cats with polycythemia vera do not show obvious clinical signs until

the PCV is very elevated; the magnitude and rate of change in PCV from low to above the normal range may be greater in CRF cats following gene therapy than that experienced by cats with polycythemia vera and consequently they might show clinical signs at a lower PCV. One cat did not respond to the therapy – we suspect that the gene was not delivered properly to the muscle, as muscle mass was severely decreased in this cachetic cat. Adjustment of the dose of the genetic material is under consideration for future studies. Hydroxyurea as used in the treatment of polycythemia vera is a chemotherapeutic agent with minimal side-effects in cats that might be useful in EPO-gene treated cats that develop persistent polycythemia.

Alternatively, genes with "on/off" switch technology could be developed. Such a method is currently under study at the University of Florida (Levy J:ACVIM Proceedings 2001) using a doxycycline sensitive regulatory element in which low doses of doxycycline are used to turn on EPO expression. Fixed dose expression of EPO was not reliable in control of hematocrit nor was surgical removal of the injection site successful in returning PCV to lower levels in all cases. This group used surgical exposure followed by EPO-gene injection of the superficial gluteal muscle.

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MANAGEMENT OF ARTERIAL HYPERTENSION IN CHRONIC RENAL FAILURE

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Systemic hypertension occurs commonly in dogs and cats with chronic renal failure when determined by methods that indirectly measure blood pressure. There are many artifacts that increase blood pressure transiently while the measurement is being taken. The "white-coat" effect refers to increased activation of the sympathetic nervous system as the cause for the temporary increase in blood pressure (which can go very high). Hypertension is commonly defined when systolic pressure is > 200 mm Hg, diastolic > 110, and mean pressure > 150 mm Hg. Borderline hypertension is suspected at > 180 mm Hg systolic pressure. Severe systemic hypertension can create endorgan damage clinically manifested as blindness (retinal hemorrhages, retinal detachments), seizures, dyspnea in cats, and epistaxis. Systemic hypertension is a major risk factor for the progression of CRF in people and rats, but this has not been established for dogs and cats with CRF. Perfusion pressure in remnant glomeruli during CRF is increased and the fear is that increased systemic blood pressure will be transmitted to the glomerular vascular beds causing further damage.

It is essential that dogs and cats be in a quiet environment before and during blood pressure measurements by either oscillometry or by ultrasonic Doppler. The averaged results of 5 consecutive and consistent oscillometric values (< 20 % variability) are recommended for dogs taken from the coccygeal artery or 3 ultrasonic Doppler values from the tarsal artery. Oscillometry in awake cats is very unreliable compared to direct measurement and a reading is not recorded in about 1/3. Ultrasonic Doppler method using the median artery is the indirect method of choice for cats.

Treatment of hypertension **SHOULD NOT BE UNDERTAKEN UNLESS** access to serial measurement of blood pressure is available. It is justified to aggressively treat hypertension as defined above, especially if there are clinical signs related to the hypertension. It is less clear if cases of CRF with less severe increases in blood pressure benefit from antihypertensive maneuvers. Single agent therapy using ACE-Inhibitors (enalapril, benazepril), calcium channel blockers (amlodipine), beta adrenergic antagonists (atenolol, propranolol), or alpha-1 adrenergic antagonist (prazosin) may lower blood pressure. Diuretics and dietary salt restriction are not effective treatment for severe hypertension. Side-effects from antihypertensives include hypotension and reduced blood flow to kidneys. In some animals, it appears that high systemic blood pressure is helping to drive GFR since when systemic hypertension is successfully treated, GRF falls and BUN and creatinine increase. In others, GFR actually increases as the level of systemic hypertension declines.

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RENAL TRANSPLANTATION IN THE DOG AND CAT – AN UPDATE

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Feasibility of Renal Transplantation

Availability of better immunosuppressive agents, improved understanding of rejection biology, improved microvascular surgical technique, and improved technique for ureteroneocystostomy all have led to improved success in renal transplantation for both dogs and cats. Greater success has been achieved in the development of transplant programs for cats compared to dogs to date. Despite thorough preparation, patient selection, and appropriate immunosuppression, some patients will experience graft failure and death. Dogs undergoing renal transplantation survived a mean of 18.3 months and a median of 8 months in a recent report from a transplant program using an aggressive regime n of immunuosuppression (KA Mathews 2000). Two dogs from this transplant program survived longer than 5 years following renal transplantation with 6 dogs surviving at least 12 months. Cats that underwent renal transplantation in another program survived a mean of 15 months and a median of 8 months (n = 28); cats that were still alive at the time of this report survived a mean of 26 months and a median of 22 months (n = 18) (Gregory 1997). The longest survival period of cats from this transplant program was 81 months (n = 2).

The concept of renal transplantation should not be undertaken lightly. Owners of dogs or cats considered candidates for renal transplantation should thoroughly understand the emotional, financial, and time commitments that are needed from them and that will be expended by the transplant team. Time and expense continue with weekly and then monthly recheck evaluations for the first year if the process has been successful. There is an emotional roller coaster during the initial transplantation efforts as one tries to balance the level of immunosuppression so as to avoid rejection but yet to avoid development of life-threatening infections. Successful renal transplantation requires a dedicated team of veterinarians with surgical and medical expertise; special interest in immunology and infectious diseases is very helpful. There are very few veterinary referral sites around the world that develop and maintain the expertise needed to offer a successful renal transplant program.

Indications for Renal Transplantation

Surgical renal transplantation does not replace failed medical management (Greogry 1998). Renal transplantation is not considered a rescue treatment for animals in the advanced stages of chronic renal failure (poor body condition scores with appreciable weight loss) as some groups consider them poor transplantation candidates. Progressive weight loss not manageable by standard conservative medical management is a major indication for renal transplatation in cats for the Gregory group at UCDavis irrespective of specific levels of renal functional parameters. The Mathews group at Guelph considers dogs candidates for renal transplantation when they are no longer responsive to either subcutaneous or intravenous fluids, have no systemic or urinary infections, no malignancies, and a urinary protein to creatinine ratio of less than 5.0. It is best to start thinking about the possibility of renal transplantation before the animals are very sick in order to avoid the "too-little too-late" syndrome.

Relative and Absolute Contraindications for Renal Transplantation – from the Recipient's Perspective

Advanced catabolism of chronic renal failure lessens the likelihood for a successful renal transplant. Efforts to improve body condition scores should be attempted prior to renal transplantation using tube gastrostomy feeding if needed. Cats with concomitant inflammatory/infiltrative bowel disease may be at increase risk for accelerated renal rejection (Gregory 1998). Cats or dogs with other major organ dysfunctions or infectious diseases are not good candidates to undergo renal transplantation. Cardiac abnormalities in cats may also be a poor indicator of long term success following renal transplantation (increased cardiac size on echocardiography, gallop rhythmms, abnormal ECG – but not murmurs). Cats with hyperthyroidism should have this corrected prior to transplantation. Animals with hypertension should have this medically controlled prior to renal transplantion (especially cats). Cats with a history of bacterial UTI (confirmed by quantitative urine culture) are not good candidates for renal transplantation due to the possibility of activation of more UTI while on immunosuppressives. A history of a previous UTI is a risk factor for recurrent bacteriuria post immunosuppression. If the history of UTI is not clear, a cyclosporine challenge for two to three weeks followed by urine culture has been suggested to ensure that bacteriuria will not be a problem in the future (Gregory 1998). Dogs are not accepted into the transplant program at Guelph during acute renal failure from ethylene glycol poisoning due to vasculitis encountered in that condition that can threaten the transplanted kidney(KAMathews 2000). Recipients that are seropositive for toxoplasmosis are at increased risk for activation of latent toxoplasmosis during immunosuppression and should be monitored closely for the development of acute toxoplasmosis (Bernsteen 1999).

Pre-Transplanatation Evaluation – Donor

The best potential donors for renal transplantation are siblings or parents but they still may not be compatible. It is not always possible to locate siblings or parents for consideration, so donors will usually be unrelated and unmatched random source animals. It is not desirable to use kidneys from related donors if the recipient's kidney disease is familial in origin. Some programs maintain a colony known to be free of infectious diseases and of known blood type that are available for donors. Other programs require that the owner provide a suitable donor often following adoption from a humane shelter. It is imperative that animals from shelters be screened intensively for infectious diseases initially and then again 8 to 12 weeks later to ensure that no infectious diseases were incubating when the animal was initially procured. It is customary to require owners to sign papers stating that they will permanently adopt donors procured from animal shelters. Multiple candidates (adoptees) may need to be screened in order to find one that will be a suitable donor. Major and minor cross-match is performed in cats between potential donor and recipient for blood compatibility. Some transplant programs only consider dogs as donors that are DNA-matched or matched by mixed lymphocyte response (Gregory); others accept DEA typed and blood cross-matched donor dogs (KA Mathews).

The donor should have two normal kidneys anatomically (ureter and vascular numbers and location) and functionally and be in excellent health for all organ systems. Routine serum biochemistry, hematology, and urinalysis should be normal. Imaging of the kidney should include ultrasound (preferably with doppler flow capability) and intravenous pyelography (IVP – to

more fully evaluate the anatomy of the ureter). In cats the donor should be as large as possible, or at least not 0.5 kg smaller than the recipient. Dog donors should be as large or larger than the recipient. Urine culture to ensure the absence of bacterial UTI should be determined. Potential donors should be seronegative for toxoplasmosis. Cats should be seronegative for feline leukemia virus (FeLV) and for feline immunovirus (FIV). Dogs should be negative for heartworm.

Pre-Transplanatation Preparation – Recipients

The anemia of chronic renal failure should be corrected so that the PCV is near the normal range prior to transplantation. This can be accomplished by treating with injections of human recombinant erythropoietin that usually result in normal range PCV within 3 to 4 weeks or by cross-matched blood transfusions. Many dogs and cats develop clinically relevant levels of anti-human recombinant eruthropoietin antibodies – whether this impacts the rejection phenomenon is unknown. Animals that have very poor body condition scores should undergo tube gastrostomy feeding to improve these scores prior to transplantation – this may take one to three months. An IV line is placed and fluids are given at rates and quantities to ensure adequate hydration and maintenance of perfusion during anesthesia and surgery. Correction of major acid-base and electrolyte abnormalities prior to transplantation is desirable.

For cats (Gregory protocol) : Cyclosporin-A is started at 5 mg/kg twice daily 24 to 48 hours prior to transplantation. Another protocol published by this group is cyclosporine at 7.5 mg/kg 24 hours prior to surgery or microemulsified cyclosporine at 3 mg/kg twice daily 24 to 36 hours post renal transplantation(JAVMA 1997). Oral cyclosporine is transferred to gelatin capsules due to the unpleasant taste and salivation that occur otherwise. Oral prednisone is started on the morning of the transplant at 0.25 mg/kg twice daily for the first 30 days and then decreased to once daily. A 12 hour trough level of whole blood cyclosporin is measured on the morning of the transplant and should be near 500 ng/ml as measured by high pressure liquid chromatography (HPLC). Whole blood levels (lysed RBC) of cyclosporine are about twice that of serum. After 3 months the cyclosporin level is targeted to approach 350 ng/ml. Tapering of the cyclosporin dosage is titrated to the biologic effect seen which may not correlate with the whole blood level. A broad-spectrum non-nephrotoxic antibiotic is given IV immediately prior to the transplant surgery. Mannitol at 1-2 gm/kg is given to the recipient cat 15 to 20 minutes prior to receiving the donor kidney in order to decrease the incidence of acute tubular necrosis (warm ischemia in the donor kidney).

For dogs (KA Mathews protocol): A combination of rabbit antidog antithymocyte serum, cyclosporin-A, azathiaprine, and prednisone is used for immunosuppression in this protocol for dogs. Antithymocyte serum is given in a gradually increasing dose from day –2 through day 6 with the goal of decreasing the lymphocyte count to 10% of baseline. On day –2 prednisone at 1 mg/kg daily is given orally and then azathiaprine is started on day –1 at 1.0 mg/kg daily orally. Cyclosporin is added on day 2 or 4 at 10 mg/kg once daily orally and the dose manipulated to maintain a 12-hour trough level of 500 to 600 ng/ml of cyclosporine when measured by monoclonal RIA. At 6 months, the targeted level of cyclosporin is 400 ng/ml, and 300 ng/ml during the second year post transplantation. The KA Mathews protocol considers the antithymocyte serum portion of the protocol to be the most important for long term success in renal transplantation in the dog. Unfortunately, antidog antithymocyte serum is not commercially available and must be raised by the local transplant group. The effect of locally raised

antithymocyte serum may vary by batch and by group due to differences in methods. Aspirin at 0.5 mg/kg orally twice daily is given to dogs in an attempt to decrease platelet aggregation (KA Mathews). Mannitol at 0.75 g/kg is given IV over 10 minutes post renal transplant to dogs while maintaining ample IV fluid infusion (30 ml/kg/hr) in minimize post-transplant renal ischemia.

Methods of Renal Transplantation

Two surgical teams operating at the same time are optimal, one working to harvest the kidney from the donor and the other to place the donor kidney into the recipient. The donor kidney needs to be in place in the recipient by 60 minutes in methods in which cooling and perfusion are not used (Gregory UCD). Either the left or right kidney may be harvested; the left kidney of dogs is preferred by some due to its relatively long renal vein (Mathews 2000). The Matthews protocol for dogs involves cold flushing of the donor kidney through the renal artery with a solution of 500 ml of saline in which 6 ml of 2% lidocaine without epinephrine and 2,000 units of heparin have been added. The renal aretery is flushed until the fluid flowing out the renal vein is clear. Microvascular surgery methods that achieve 3-10 times magnification are required for anastamosis of vessels in the cat. Magnification is not essential in larger dogs but it still is helpful to facilitate the surgery. The donor kidney is placed in the iliac fossa. The vessels of the donor kidney are anastamosed to the iliac artery and vein by a variety of end to end (renal artery) or end to side (renal vein) methods. The arterial end to side technique in cats appears to be the superior method for renal transplantation in cats as it required less surgery time, was not associated with pelvic limb vascular flow problems, and had good return of renal function (Bernsteen 1999). Vascular clamping methods have improved this process for some groups (Degner), though traditional vascular suturing is still successful. Ureteroneocystosomy is then performed – adjustments in technique have dramatically reduced episodes of obstruction or leakage that occurred with earlier techniques in cats (change from drop in technqiue to a mucosal appositional technique). Ureteroneocystostomy is considerably easier in dogs than in cats. The native kidneys of cats are usually left in place to provide some level of support for renal function, unless upper urinary tract infections, severe hypertension, or large cysts of polycystic renal disease are creating problems. The native kidneys of most dogs are removed during the transplant surgery due to systemic arterial hypertension associated with the diseased kidneys (KA Mathews). A gastrostomy tube should be placed at this time if one is not already in place.

Following the Transplant Patient

The donated kidney should become engorged with blood followed by a vigorous flow of urine shortly after the vascular anastamoses have occurred. Hypothermia, hypotension, and anemia (blood loss) are immediate concerns following completion of the renal transplantation that can adversely affect the newly placed kidney by reducing its perfusion. Good post-operative nursing care and fluid therapy are essential to prevent reduced renal perfusion. If the graft is functioning properly, the serum creatinine should rapidly decline. Serum creatinine may be within the normal range within 24 hours for those with modest pre-transplant increases and by 3 days for those with higher levels of pre-transplant azotemia.

Urinary specific gravity should increase to greater than 1.020 and the serum creatinine should decrease to normal levels by 3 days post-transplantation in cats (Gregory). Otherwise concerns exist for renal ischemia (vascular, warm ischemia, hypotension resulting in acute tubular necrosis), ureteral obstruction, or leakage of urine from the newly implanted ureter.

PCV/TP , serum creatinine, urinalysis, and whole blood cyclosporine levels should be evaluated weekly for the first month and then every 3 to 4 weeks if adequate management has occurred by this time. Trough whole blood cyclosporine levels are important to follow as there is tremendous variability in oral absorption of cyclosporine; cyclosporine levels may display little correlation to dose. The initial levels of cyclosporin are stable by 14 to 21 days in dogs (KA Mathews). The dose of cyclosporine is decreased after the first several months. The blood concentration of cyclosporine may not change despite a decrease in dose due to increased bioavailability over time. A new microemulsion form of cyclosporine (Neoral®-Sandimmune) apparently provides more consistent intestinal absorption and less variability in blood levels. Remember that conurrent drug therapy can dramatically influence whole blood cyclosporine concentrations. For example, the use of phenobarbital results in lower concentrations and the use of itraconazole or ketaconazole increases the level of cyclosporine through effects on hepatic metabolism.

CBC and serum biochemistry need to be assessed periodically to evaluate the effect of azathiaprine on the bone marrow (cytopenia?) and liver (increased liver enzymes and or decreased liver function?) for the immunosuppressive protocol in dogs.

The transplanted kidney can be followed by doppler studies during ultrasound, quantitative scintigraphy, GFR by exogenous creatinine or iohexol clearance, low dose DTPA or MAG3 nuclear medicine clearance, urinary enzyme measurement, or punch biopsy when it is unclear how well the graft is doing.

Complications Following Renal Transplantation

Seventy-one percent of cats (47/66) undergoing renal transplantation were discharged from the hospital in one report. The most common causes of death in cats after release from the hospital were renal failure and related complications (32%), immunosuppression related disease (29%), and cardiac disease (11%). Three of 15 dogs receiving renal transplants died due to surgical complications (20%) and 4 died (27%) due to allograft rejection (1-12 months later).

Seizures, depression, and coma followed by death have affected some cats in the first few days following transplantation; seizures occurred in approximately 20% of all transplanted cats in one study (Gregory 1997). Consequently it is important to vigorously monitor the neurologic status of cats for 24 to 48 hours post transplantation. Mannitol at 0.5 to 1.0 g/kg IV every 30 to 60 minutes has been suggested as rescue treatment in these instances. More recently, severe systemic hypertension was found to be a major complication contributing to post transplant seizures in cats (Kyles 1999). Treatment with hydralazine reduced systolic pressure to < 170 mm Hg within 15 minutes and dramatically reduced the frequency of post transplant neurologic complications.

Vascular thrombosis can occur up to 72 hours post-vascular anastamosis. Ureteral obstruction can be a problem when older technique for implanting the new ureter is employed, especially in cats.

Bacterial urinary tract infections can be acquired; urine culture is recommended weekly for the first 4 weeks by the Mathews group. Treatment of UTI in those on cyclosporine requires

special attention to which antibiotics are chosen – aminoglycosides and potentiated sulfas are to be avoided. Lethal systemic bacterial, fungal, and protozoal infections can occur and may be associated with too high a trough level of cyclosporine needed for maintenance of the graft. All dogs on the cyclosporin, azathiaprine, prednisone, and antithymocyte serum protocol for immunosuppression developed infections. Cancer presumptively occurred secondary to the immunosuppressive protocol in one dog and in 2 cats.

Peracute rejection occurs when preformed antibodies in the recipient react against antigens in donor cells especially those in endothelium. This has not been recognized yet in dogs or cats. If it does occur, the graft is destroyed within hours.

Cytotoxic T-lymphocytes are the primary mechanism of renal destruction during acute rejection; mononuclear cell infiltration is typical on renal biopsy in these instances. Acute rejection is most likely to occur during the first month post transplantation; clinical signs may or may not be apparent. Enlarged painful kidneys may be present in association with an increase in the serum creatinine. A sudden increase of serum creatinine by as little as 0.3 mg/dl is cause for concern in a well-hydrated patient. Enlarged hypoechoic kidneys may be discovered during renal ultrasonography. Depression, anorexia, vomiting, proteinuria, and hematuria are variable findings. Acute rejection is usually associated with cyclosporine levels that are too low. With acute rejection in cats and cyclosporine levels less than 150 ng/ml, aggressive rescue treatment is indicated with IV cyclosporine (6-8 mg/kg IV over 4-6 hours daily) and IV prednisone (10 mg/kg twice daily) until the serum creatinine substantially declines. Oral medicines are resumed at higher doses that were associated with better immunosuppression. A protocol for rescue from acute rejection in dogs suggests treatment with IV methylprednisolone at 10 mg/kg, 7.5 mg/kg, and then 5 mg/kg on 3 successive days while the doses of cyclosporine and azathiaprin are returned to the previous higher doses in which rejection was not a problem (KA Mathews).

Nephrotoxicity and hepatotoxicty of cyclosporine can be seen in humans, but is rarely observed in dogs or cats. Cyclosporin induced nephrotoxicity has been suspected in experimental dogs which underwent renal transplantation; it was reversible when cyclosporin was discontinued (Kelly 1986).

Chronic rejection is suspected when serum creatinine concentration continues to gradually increase over months to years in association with reduction in renal mass (serial ultrasound). This can occur with or without previous episodes of acute rejection. Infection of the transplanted kidney can also cause loss of renal function but the kidney is usually normal size to enlarged. Proteinuria and hematuria can be encountered in the chronic rejection process as with acute rejection. Renal biopsy can be used to more definitively determine acute from chronic rejection. Alternatively, challenge treatment with an acute rejection rescue protocol of immunosuppression can be implemented to see if improvement in renal function occurs (acute rejection). Chronic rejection is often associated with intimal thickening of arterioles.

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Renal Insufficiency and Hyperthyroidism in Cats

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Renal insufficiency and hyperthyroidism are relatively common conditions of older cats. It can be difficult to accurately diagnose cats with chronic renal failure, hyperthyroidism, or both conditions as there are many overlapping clinical signs (weight loss, polydispsia, polyuria, dilute urine). It is likely that hyperthyroidism is underdiagnosed in cats with chronic renal failure since nearly half of cats with CRF and hyperthyroidism will have a normal T4 level on a single measurement. The relationship between the development of hyperthryoidism as a consequence of renal insufficiency has not been explored. The possibility that hyperthyroidism causes chronic renal disease in some cats has received little attention. Most attention has focused on the simultaneous occurrence of renal insufficiency and hyperthyroidism in a population of cats under consideration for treatment of hyperthyroidism. It has been observed that a population of hyperthyroid cats develop azotemia or display a worsening of azotemia following therapy that induces euthyroidism.

Thyroid hormones exert major effects on renal functions. Normal cats undergo increased GFR and RBF and decreased BUN and serum creatinine following thyroxine injections for 30 days (Adams 1997). Groups of cats with hyperthyroidism often have increased GFR compared to normal cats. Plasma iohexol clearance in 12 hyperthyroid cats was 3.83±1.82 ml/min/kg (N = 13) compared to normal cats at 1.83 ± 0.56 ml/min/kg (n = 10) (Becker 2000). Similar results were found when GFR was determined using DTPA clearance nuclear medicine (2.51±0.69 ml/min/kg in 13 hypethyroid cats vs 2.02 ± 0.27 ml/min/kg in 11 normal cats) (Graves 1994) . Hyperthyroidism is known to result in dilute urine and polyuria with polydipsia. This effect is likely due to increased RBF and medullary solute washout, though a direct effect on the collecting tubules and ADH receptor interaction cannot be excluded. Psychogenic mechanisms also cannot be excluded. Hyperthyroidism is known to result in hypercalciuria in other species due to enhanced bone calcium mobilization; this effect may have some role in the development of polyuria as well as a possible role in creating chronic renal damage by excessive exposure of renal tissue to calcium. Most cats with hyperthyroidism also have increased systemic blood

pressure, which could injure renal tissue. Hyperparathyroidism was noted in 77% of 30 cats with untreated hyperthyrodism; the magnitude of increased PTH levels was very large in some instances (Barber 1996). The reversibility of hyperparathyroidism following correction of hyperthyroidism has not been reported. Though serum creatinine (and calcium) was lower in this population of hyperthyroid and hyperparathyroid cats, the possibility of renal secondary hyperparathyroidism cannot be excluded (renal disease may still exist and not be detected).

Hyperthyroid cats (n = 12) decreased GFR (iohexol clearance) from 3.83±1.82 to 2.02 ± 0.81 4 to 6 weeks following treatment with methimazole (Becker 2000). Two of these 12 cats developed overt azotemia following treatment in this same study though as a group increases in BUN or serum creatinine did not achieve statistical significance. Twenty-two hyperthyroid cats treated with radioiodine experienced no change in GFR, BUN, or creatinine 6 days following treatment (T4 was decreased), but BUN and creatinine were significantly increased at 30 days (T4 was also further lowered) (Adams 1997). No cats with a GFR > 2.25 ml/min/kg developed post treatment renal failure in this same study. Thirteen of 15 cats with GFR < 2.25 ml/min/kg were in renal failure 30 days following radioiodine treatment (2/15 that failed to suppress T4 did not develop azotemia); 9 of these 15 were azotemic prior to treatment; the others had normal paramters initially (Adams 1997). GFR (DTPA nuclear clearance) decreased from 2.51 ± 0.69 ml/min/kg to 1.40 ± 0.41 ml/min/kg 30 days following bilateral thryoidectomy in 13 cats (Graves 1994) while creatinine increased from 1.26±0.34 to 2.05±0.60 and BUN increased from 26.62±6.83 to 34.92±8.95.

Azotemia prior to treatment of hyperthyroidism was detected in as many as 41% of cats and in 59% of cats 30 days post treatment in one study (Adams 1997). Twenty-three percent developed azotemia for the first time following treatment in the same study. Mean serum creatinine and BUN increased at 30 and 90 days post-treatment in 58 cats treated by surgery, methimazole, or radioiodine; there were no differences in the magnitude of increase by treatment group (Dibartola 1996). Nine of these 58 cats had increased serum creatinine concentration prior to treatment. Two of 12(Becker 2000) and 2 of 13 (Graves 1994) cats developed overt azotemia following treatment with methimazole or bilateral thyroidectomy respectively. Based on results of these three studies, it appears that an estimate for the development of de novo azotemia

following treatment for hyperthyroidism in cats is from 15-23%. Some increase in serum creatinine concentration is expected following the development of euthyroidism due to increased muscle mass (origin of creatinine), though decreased GFR certainly contributes to increased serum creatinine concentration. It is likely that lessening the degree of hyperthyroidism results in decreased RBF and GFR that unmasks azotemia in cats with marginal renal function prior to therapy.

Should cats with overt azotemia and hyperthyroidism be treated for hyperthyroidism ? It is likely that many of these cats will increase their level of azotemia following treatments that result in euthyroidism. In some cats this increase in creatinine will be mild, while other cats will experience large increases in serum creatinine. If clinical signs related to hyperthyroidism are severe, at attempt at treatment is warranted. We recommend screening cats with obvious azotemia and those suspected of renal disease with a methimazole challenge. Methimazole treatment provides a reversible means of inducing euthyroidism and observing what happens to the level of renal function. An initial dose of 2.5 mg BID is given for 2 weeks and then serum biochemistry is repeated to evaluate renal function and T4 levels. If renal function is stable, the dose is gradually increased every two weeks as needed until T4 levels have entered the normal range if renal function remains stable. The dose can be increased to 2.5 mg TID, then 5 mg BID, and 5 mg TID if needed. Methimazole is discontinued if renal function deteriorates during the methimazole challenge. If renal function remains stable, then long term methimazole can be considered for therapy or more-definitive treatment of hyperthyroidism provided by I-131 treatment or surgery. The definition of "stable" renal function is arbitrary and in our hospital means that the creatinine increased less than 2.0 mg/dl in those without initial azotemia and less than 1.0 mg/dl in those with obvious azotemia.

Supplementation with thyroxine should be considered for those cats with renal disease that become hypothyroid following bilateral thyroidectomy or radioiodine treatment. Anecdotal evidence suggests that excretory renal function can be supported in some post-treatment hypothyroid cats when supplemental thyroxine is supplied. As a compromise, it may be desirable to titrate the dose of methimazole in cats with marginal renal function in such a way as to

partially control the hyperthyroidism without decreasing GFR too much. Other treatments to control cardiac effects of uncontrolled hyperthyroidism may be warranted (beta blockers).

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IDIOPATHIC AND INTERSTITIAL CYSTITIS in CATS

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Idiopathic cystitis was the most-common diagnosis (64%) in our series of cats with signs of lower urinary tract disease, as has been the case in other series over the past 4 decades. Urolithiasis of all types comprised approximately 15% of the cases (7% struvite, 6% oxalate, and 1% unknown), anatomic defects (urachal diverticulum, urethral stricture) at 11% and behavioral abnormalities at 9% were next in frequency. Diagnosis of urinary tract neoplasia and bacterial urinary tract infection was very uncommon. These data were collected from our referral center and should be interpreted with caution to predict frequency of diagnosis in a primary care practice.

Terminology referring to disorders of the feline lower urinary tract has been confusing. Widespread use of the term FUS (feline urologic syndrome) often was used indiscriminately to describe cats with signs of irritative voidings regardless of underlying cause. The term FLUTD (feline lower urinary tract diseases) was subsequently coined to shift focus to the fact that many diagnosable lower urinary tract diseases exist in cats. The term idiopathic lower urinary tract disease is appropriate if no cause of irritative voiding signs is found following a complete exclusionary diagnostic workup that includes urinalysis, urine culture, and urinary imaging with some combination of radiographs, contrast cystography, contrast urethrography, and ultrasonography of the bladder. Use of the term feline interstitial cystitis (FIC) as an umbrella term for all cats with idiopathic LUTD is not appropriate. The term feline interstitial cystitis is reserved for those cats that have frequent recurrences of clinical signs or persistence of clinical signs chronically. Idiopathic cystitis can be acute or chronic, but interstitial cystitis by definition is a chronic process. Furthermore, the use of this term should be restricted to those in which cystoscopic evaluation of the bladder and urethra has been performed following exclusionary diagnostic workup. Cats usually are not subjected to extensive diagnostic testing after an initial episode of lower urinary tract signs. Consequently, most of our data on idiopathic or interstitial cystitis have been collected from cats with recurrent disease. Data are especially lacking from primary care veterinary practices as most epidemiological studies have been conducted at referral centers.

Idiopathic cystitis is a disease of irritative voiding signs (dysuria, pollakiuria, hematuria, urination in inappropriate locations), bacteriologically sterile urine, urine that contains epithelial cells without cellular atypia (if any epithelial cells at all), and failure to find a more objective cause for this clinical picture after appropriate lower urinary tract diagnostic procedures including plain and contrast radiography or ultrasonography. The diagnosis of idiopathic cystitis is a diagnosis of exclusion. Idiopathic cystitis is classified as a non-infectious inflammatory lower urinary tract disease. Inappropriate urination was the most common owner-reported clinical sign in our series of cats with idiopathic cystitis. Most cats with non-obstructive idiopathic cystitis spontaneously resolve their clinical signs within 5 to 7 days regardless of treatment, though signs recur in about 50% of cases. A small group of cats affected with idiopathic cystitis continue to display signs of inflammation either continuously or intermittently. Urethral obstruction develops in some males secondary to the inflammatory process within the bladder and urethra. Whether this is a self-limiting disease or a chronic disorder with acute attacks remains to be determined. Some affected cats have a striking increase in severity of clinical signs that appear to be associated with stress, while others display waxing/waning of clinical signs without known change in stress. A number of cats with idiopathic cystitis qualify for a narrower diagnosis of interstitial cystitis if characteristic submucosal hemorrhages ("glomerulations") are observed during cystoscopy following bladder distension to 80-cm water pressure in the absence of other diagnoses. We estimate that 40% of the cats with an initial

diagnosis of idiopathic cystitis studied with cystoscopy will display such glomerulations; the remaining cats display other lesions supportive of cystitis, including increased vascularity, edema, and exaggerated mucosal friability.

Dysuria, stranguria, pollakiuria, macroscopic hematuria, and urinating in places other than the litterbox (inappropriate urination) are non-specific signs that, individually or in some combination, cause clients to bring their cats to a veterinarian due to apparent non-obstructive problems with the lower urinary tract regardless of the underlying cause. Inappropriate urination was the most common owner-reported clinical sign in our series of cats with idiopathic cystitis, occurring in nearly 98% of females and 87% of males. Episodes of inappropriate urination occurred more than 6 times per week in 70% and 3 to 6 times per week in 13% of both males and females. Increased frequency of urinations was the next most commonly observed clinical sign, occurring in nearly 80% of both females and males. Stranguria was noted in 65% of females and 75% of males. Macroscopic hematuria was reported least frequently, occurring in 58% of females and 67% of males; frequent episodes of hematuria were reported in about 50%[Buffington, 1997 #80]. It is important to recognize that many cats exhibiting inappropriate urinations as the sole owner complaint actually have idiopathic cystitis, rather than a behavior disorder. When examined with a cystoscope, we found that 16/24 cats with the single owner complaint of inappropriate urinations actually had IC rather than a pure behavior disorder.

A specific diagnosis that accounts for lower urinary tract signs requires integration of findings from history, physical examination, urinalysis, urine culture, survey and contrast radiography, ultrasonography, urethroscopy, and cystoscopy (see algorithm at end). It is important initially to decide if the cat's diagnosis fits into one of 3 categories: organic/functional bladder disease, behavior problem, or polyuric disorders.

PATHOPHYSIOLOGY

Cats with FIC have abnormalities of local bladder factors, sensory (afferent) neurons, the central nervous system, and sympathetic (efferent) neurons. Bladder abnormalities include decreased urinary glycosaminoglycan (GAG) excretion, histologic changes, increased bladder permeability, and neurogenic inflammation. Histologic changes are typically nonspecific, but submucosal hemorrhage and increased numbers of mast cells may be present. The neurotransmitter substance P, and the density of the high-affinity substance P receptor are increased in the bladder of cats with FIC, which may increase an inflammatory response. Abnormalities of both the central and peripheral sympathetic nervous system have been identified in cats with FIC. For example, significant increases in tyrosine hydroxylase immunoreactivity have been identified in the locus coeruleus (LC). Possibly as a consequence of increased LC output, cats with FIC have increased stimulus-induced local NE release from the bladder and down-regulation of central and peripheral alpha-2 adrenoceptors (AR). In the detrusor, beta-1 AR are downregulated, and beta-3 AR appear to restore some of the missing beta-1 function. In normal cat spine, α-2 agonists inhibit transmission of noxious afferent signals to the brain. The receptors appear to be located on the central processes of sensory neurons. Although spinal α-2 AR activation can inhibit nociceptive input acutely, these receptors seem to become downregulated after chronic stimulation. In contrast to the apparent activation of the sympathoneural system, abnormalities of the hypothalamic-pituitary-adrenal axis have not been reported, suggesting the sympathoneural activation is not just the consequence of a generalized stress response. Abnormalities in the central nervous system may explain the limited success of FIC therapies solely directed at the bladder.

Treatment of Idiopathic and Interstitial Cystitis

Because the underlying cause(s) of this disorder are unknown, treatment recommendations must necessarily be tentative. A combination of recommendations is usually offered that include a discussion of litter box management, how to clean soiled areas, and what normal cat behaviors and activities might benefit this cat. Changes in diet, increased water intake, provision of pain relief, and drug therapy are also considered. Patients with interstitial cystitis are unusually susceptible to changes in their environment, one of which may be abrupt diet changes. Increasing water intake to dilute urine and increase frequency of urination is an important part of treatment. One mechanism for this benefit may be the dilution of the noxious components of urine that gain access to the bladder wall as a result of increased bladder permeability.

Dietary Treatment

Some diet modifications may reduce the risk of recurrence of lower urinary tract signs in cats with idiopathic cystitis. Since struvite crystals do not appear to damage normal urothelium, dietary efforts to reduce struvite crystalluria are not warranted in idiopathic or interstitial cystitis. Efforts to acidify the urine have no known value in the treatment of cats suffering from idiopathic cystitis. There is experimental evidence that highly acid urine increases sensory nerve fiber transmissions that increase pain perception; consequently cats with idiopathic cystitis should not be blindly placed on acidifying diets.

Pending future improvements in understanding of the pathophysiology/etiology, dietary treatment recommendations for cats with idiopathic cystitis include consideration of the constancy, the consistency, and the composition of the diet. *Constancy.* Our clinical experience suggests that diet change can result in recurrence of signs of idiopathic/interstitial cystitis in some patients. Moreover, with the advent of many similarly formulated veterinary and commercial foods marketed for use in cats with lower urinary tract signs, signs sometimes recur when cats are switched from any of these foods to another one of them. These observations suggest that diet change may result in recurrence of signs. This hypothesis is strengthened by the observation that some cats with lower urinary tract signs appear to be sensitive to a variety of environmental stimuli[Jones, 1997]. Pending further study to test this hypothesis, limiting the frequency of diet changes in this group of patients may be prudent. *Consistency* Compared with results from US household surveys, cats with idiopathic cystitis were significantly more likely to eat dry food exclusively[Buffington, 1997]. We recently reported that lower urinary tract signs recurred in only 11% of idiopathic cystitis cats during a year of feeding the canned formulation of a veterinary food designed to result in production of an acidic urine[Markwell, 1999]. Recurrence occurred in 39% of cats fed the dry form of the food, suggesting that both constancy and consistency (increased water intake) may be important, although the reasons for this effect remain to be determined. Both diets contained a similar potential renal solute load and resulted in a similar degree of urinary acidification. Interestingly, the urine specific gravity of cats fed the dry form was usually greater than 1.050 (mean of 1.050), whereas that of canned fed the canned diet usually was less than 1.040 (mean of 1.030). It appears that the canned form protected nearly 90% of cats against recurrence of lower urinary tract signs for up to one year, constancy of diet protected about 60%, and 10% were offered no protection from recurrence by the diet.*Composition* In addition to water, diet-related decreases in urine magnesium, and/or increases in urine calcium, potassium, and/or hydrogen ion concentrations all could influence activity of sensory nerve fibers in the urothelium[Maggi, 1993]. Unfortunately, most of these effects have been studied using in vitro experimental systems. The effects of urine electrolyte content on lower urinary tract signs have not been adequately studied, but may be important in treatment of some patients.

Cats suffering idiopathic cystitis seem to benefit from provision of a single, canned diet, if such a feeding plan is not too stressful to the cat or the owner. The issues surrounding stress, diet change and disease currently are controversial, and further investigation of these relationships is needed.

Amitriptyline

In severe recurrent cases, administration of the tricyclic anti-depressant amitriptyline may be considered. We recently reported the results of amitriptyline treatment in 15 cats with severe recurrent interstitial cystitis[Chew, 1998]. Failure during this study was defined as the recurrence of any lower urinary tract sign during the next 12 months. Amitriptyline successfully eliminated clinical signs of interstitial cystitis in 73% of the cats for the first 6 months, and in 60% of cats studied for the entire 12 months. Despite clinical remission, cystoscopic abnormalities persisted in all cats at the 6 and 12-month evaluations. Weight gain, somnolence, decreased grooming, and transient cystic calculi were observed in some cats.

Should amitrtipytline be used in some cats with idiopathic or interstitial cystitis? In the absence of alternative treatment, the answer is a qualified yes. We consider the use of amitriptyline only for treatment of chronic idiopathic cystitis in which other "standard" therapies have failed (client education about feeding and litterbox management, stress, and methods to increase water intake are the standard in our hospital). There is not a good argument to use amitriptyline in acute cystitis since spontaneous resoluton of clinical signs often occurs within a few days and complete resolution within 5 to 10 days and it may take weeks to months for amitritpyline to exert a maximal effect. Further studies of amitriptyline for safety and efficacy during treatment of idiopathic lower urinary tract disease are needed, though amitriptyline has been used with apparent safety in cats by animal behaviorists for many years. CBC and serum biochemical panels in our series remained normal throughout one year. Given the success of our non-placebo controlled study, double-blind placebo controlled studies using amitriptyline treatment for cats with chronic idiopathic lower urinary tract disease are warranted. Although amitriptytline has its place in the control of the signs of chronic lower urinary tract disease associated with interstitial cystitis in cats, it is not an ideal drug since the lesions of cystitis are still apparent cystoscopically during treatment and some undesirable side effects occurred in some cats. It is conceivable that lower doses of amitriptyline may be effective when given in combination with other drugs.

Amitriptyline was recently studied in cats with acute non-obstructive idiopathic lower urinary tract disease (Kruger ACVIM abstracts 2001). Cats received 5 mg per cat once daily for a total of 7 days. Compared to placebo, cats treated with amitriptyline reduced the duration of pollakiuria but clinical signs recurred sooner and with higher frequency as noted at recheck evaluations at 6,12, and 24 months following initial discharge. It is difficult to understand how such a short course of amitriptyline could exert such a long-term effect.

Glycosaminoglycans

Glycosaminoglycan (GAG) replacement therapy has been used in humans with interstitial cystitis, with a success rate in about 10-20% of patients. GAG replacement therapy currently is being investigated because of the abnormalities observed in GAG excretion and bladder permeability in affected cats. The assumption for use of this treatment is that administered GAG attaches to the defective urothelium, thereby decreasing bladder permeability, although there may be differences in the relative efficacy among the various GAG's in producing this effect[Nickel, 1998]. Glycosaminoglycans also can exert analgesic and anti-inflammatory effects that might prove useful. A double-blinded placebo-controlled multicenter study of a specific GAG treatment (pentosan

polysulfate) for cats with interstitial cystitis has recently been concluded in the USA – FDA approval is pending.

Based on evidence in humans with IC, and the absence of demonstrated efficacy of any of the current veterinary GAG preparations, we cannot recommend this as part of routine therapy for FIC. If this treatment is used, a powder form that can be added to the food should be used to avoid the stress of pill administration.

Antibiotics/Antiviral Agents

Most cats with LUT signs do not have bacterial UTI, and there is no evidence that antibiotics are useful in the initial management. Bacterial infection frequently is erroneously diagnosed in cats with idiopathic cystitis, due to failure to perform quantitative urine cultures, and the tendency to over-interpret "bacteria" reported on urinalysis. No conclusive evidence has yet emerged from cats with idiopathic or interstitial cystitis that viruses play any role in its pathophysiology, so the use of antiviral agents is also not recommended.

Miscellaneous

In preliminary studies, oral interferon, antibiotics, glucocorticoids, and intravesical DMSO treatments have not been helpful in the alleviation of clinical signs compared to placebo.

It is likely that pain plays an important role in potentiating or perpetuating inflammation of the bladder in cats with chronic idiopathic cystitis. Efforts to break the cycle of pain-inflammation-pain may be helpful in treatment of some cats. One of amitriptyline's beneficial effects is to decrease sensory nerve fiber transmission. Amitriptyline appears to provide analgesia for some cats. Butorphanol has been used by the authors for the relief of bladder pain with apparent success in a small number of cats with chronic idiopathic cystitis. Longer-term studies on the effect of chronic pain relief as therapy for idiopathic cystitis are needed. There is a regrettable lack of guidance in the treatment of chronic visceral pain.

Adjunctive Therapy

Our bias is that stress is very important in the development of flares in cats with chronic idiopathic cystitis and may be important in exposing the first episode of symptomatic idiopathic cystitis. It is unlikely that stress by itself in the presence of an otherwise completely healthy lower urinary tract leads to this disease. Unfortunately, stress is difficult to quantitate objectively or in the laboratory. Detailed history designed to reveal stress is necessary to expose "stressors" in a cat's life. Stress may result in changes in activity, use of the litter pan, dietary intake, and other factors difficult to assess. Stress manifests itself in a variety of neuroendocrine responses that could modulate the degree of inflammatory response in the bladder (and other tissues as well). Regimens to reduce stress may prove essential in the management of cats with non-obstructive idiopathic cystitis. See figure on neurogenic inflammation at end of notes.

Reduction of the cat's perception of stress is warranted. Potential sources of stress include the physical environment, other animals, and owners. Since many cats with FIC seem to be more reactive than usual (increased sympathetic nervous system outflow), providing separate, secluded food, water and litter containers for patients in multi-cat households may be appropriate.

Recently, a pheromone that exerts a calming effect on cats has become available to veterinarians. This product (Feliway ®) is a synthetic analogue of a naturally occurring feline facial pheromone. Cats release such pheromones during facial rubbing when they feel

comfortable in their environment. Although not specifically tested in cats with FIC, treatment with this pheromone has been reported to reduce the anxiety experienced by some cats in unfamiliar circumstances. It is conceivable that use of products that reduce anxiety (and associated sympathetic nervous system outflow) could be useful in treatment of interstitial cystitis.

Behavior Problem

Cats with a true urinary behavior disorder have a history of inappropriate urinations without evidence of irritative voiding (no pollakiuria, gross hematuria, vocalizing during urinations, dysuria or strangruia). Abnormal locations of urinations may be on either horizontal or vertical surfaces[Marder]. Urinalysis should not exhibit excess blood or protein and no opaque calculi are seen on survey radiographs. Radiographc contrast procedures (i.e., cystography and urethrography) are normal as is the ultrasonographic evaluation of the bladder. Cystoscopic evaluation of the bladder also should be normal. Fourteen of the 70 cats with idiopathic cystitis in this series would have been diagnosed as having a behavior disorder if they had not been examined using contrast radiograpy or cystoscopy. Unfortunately, in the absence of access to cystoscopic evaluation, cats with a normal diagnostic workup including constrast radiography will be diagnosed with a behavior disorder when in reality nearly half actually have evidence of bladder inflammation when evaluated by cystoscopy. When examined with a cystoscope, we found that 16/24 cats with the single owner complaint of inappropriate urinations actually had IC rather than a pure behavior disorder. It is interesting to note that nearly 40% of cats being treated for a urinary behavior disorder also had a previous history of cystitis[Horwitz]. There appears to be a cross-over between urinary behavior and inflammatory disorders of the lower urinary tract. One common connection is the ability of stress to incite or perpetuate either condition.

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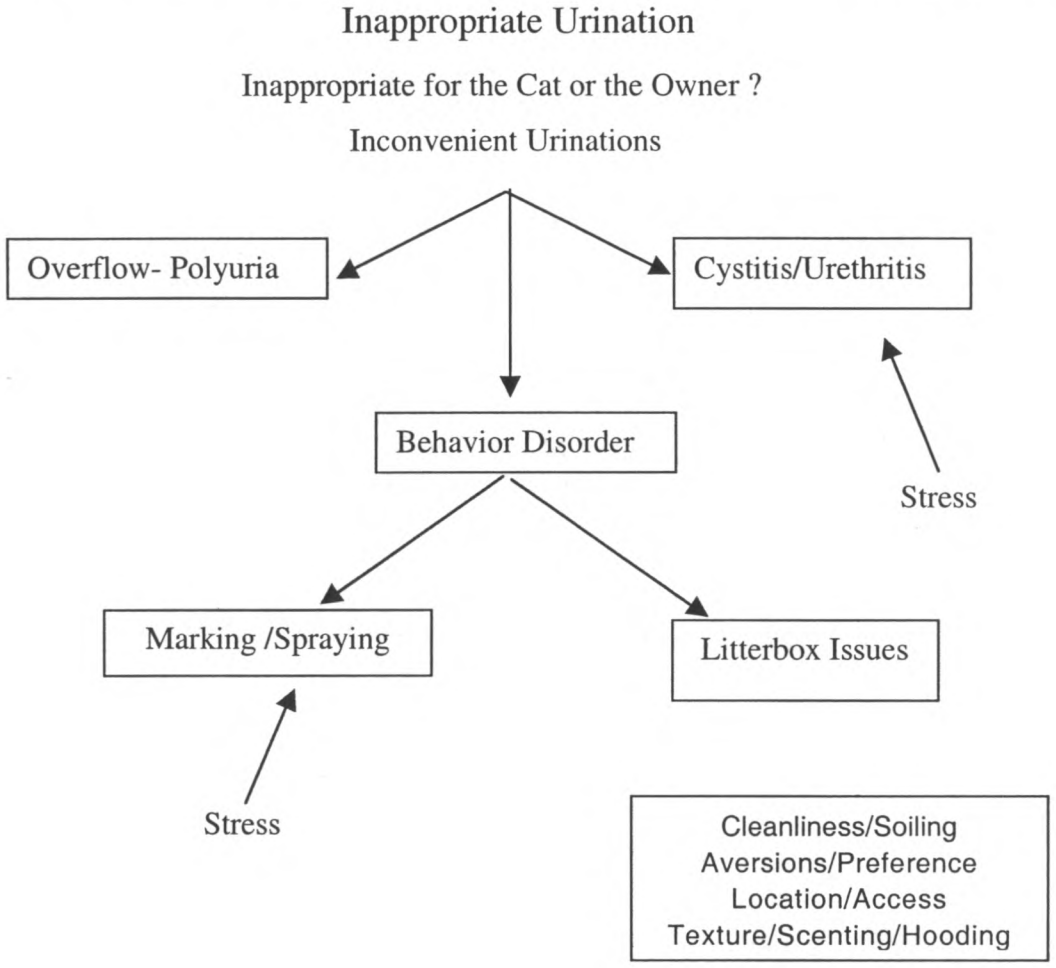
Scrivani PV, Chew DJ, Buffington CAT, Leveille R, Kendall MS : Results of Retrograde urethrography in cats with idiopathic, nonobstructive lower urinary tract disease and their associations with pathogenesis : 53 cases (1993-1995). J Am Vet Med Assoc 211(6):741-748, 1997.

Figure 1. Inappropriate urinations may be the sole complaint noticed by the owner of a cat affected with overflow from dilute urine and polyuria (renal failure, hyperthyroidism, diabetes mellitus), cystitis/urethritis (idiopathic, mechanical due to stones, bacterial infection), or with a behavior disorder. Behavior disorders should further be characterized into those that are related to marking or spraying as contrasted to those with normal eliminations that do not occur in the litterbox. Stress can activate episodes of marking or spraying as well as idiopathic cystitis.



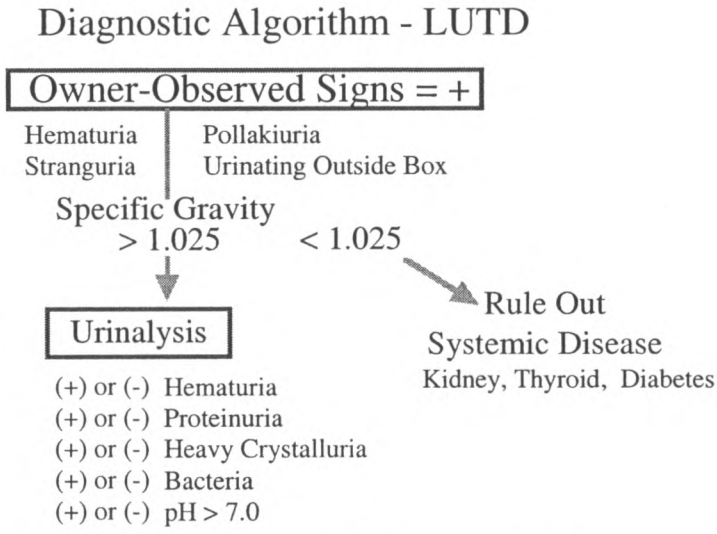


Figure 2-A. It is important to rule out dilute urine as a cause for increased urine production as a cause for inappropriate urinations. Cats consuming dry food usually have a urinary specific gravity in excess of 1.030 while cats eating canned foods may have specific gravity near 1.025. Although the presence of hematuria and proteinuria are often present during active states of inflammatory lower urinary tract diseases of cats, the severity of hematuria and proteinuria can wax and wane (false negative finding). False positive findings for hematuria and proteinuria can occur when urine samples are obtained by cystocentesis or urinary catheter. Heavy crystalluria is an uncommon occurrence in urine from cats of the 1990's in the United States. It is important to make sure that the finding of crystalluria is not over interpreted since crystals by themselves do not create disease. Crystalluria can be an artifact of urine that has cooled and sat for prolonged periiods – this is especially true for refrigerated samples. The finding of "bacteria" should be viewed with caution as there are many artifacts in feline urine that resemble bacteria. Bacteria in the presence of hematuria and pyuria more likely do reflect bacterial infection, though this is very uncommon in young cats with signs of lower urinary tract disease. Alkaline urine by itself is not a disease and is not a common finding in cats fed acidifying diets common in the 1990's.

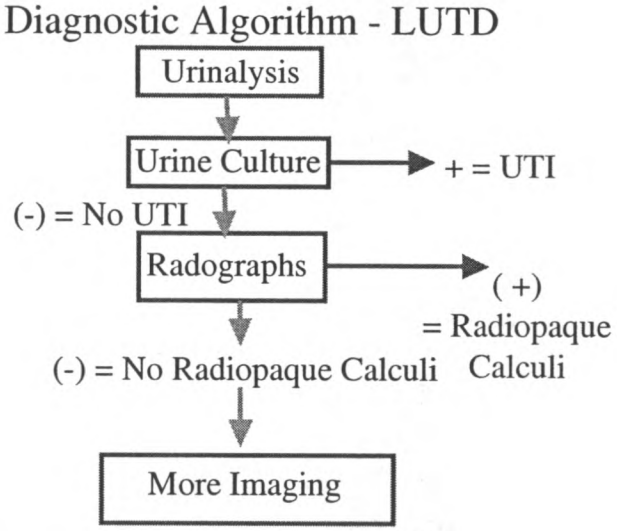


Figure 2 B

Urine should be submitted for culture if there is evidence for pyuria, there is dilute urine (<1.030), the cat has previously undergone urethral catheterization, or if the cat has had a perineal urethrostomy. Plain radiographs have a good chance toshow radiopaque calculi due to calcium oxalate or struvite, but good technique and cleansing enemas are needed to allow visualization of small stones/

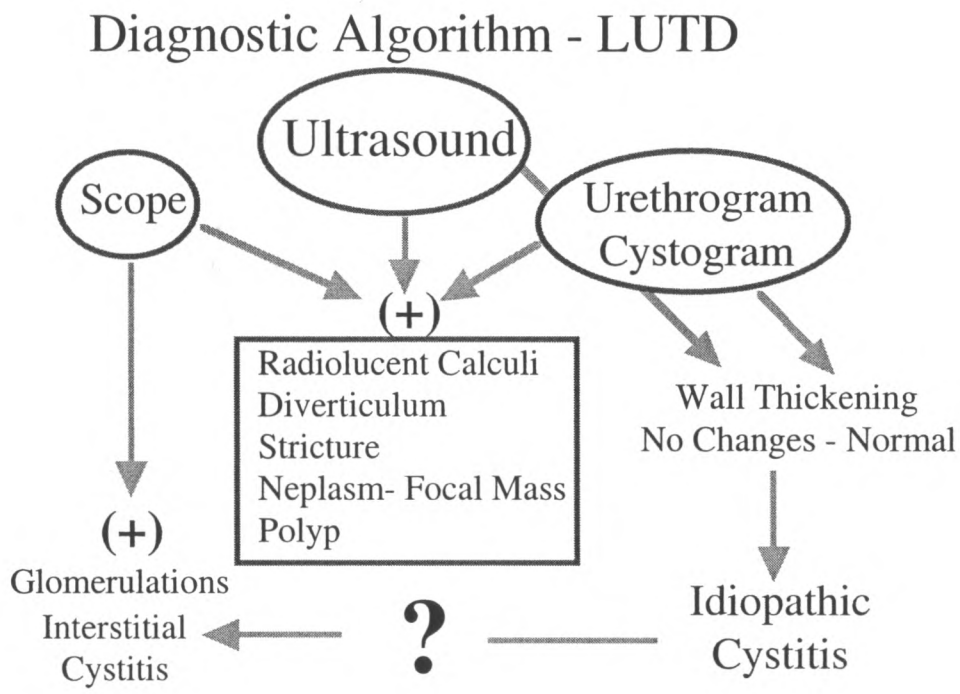
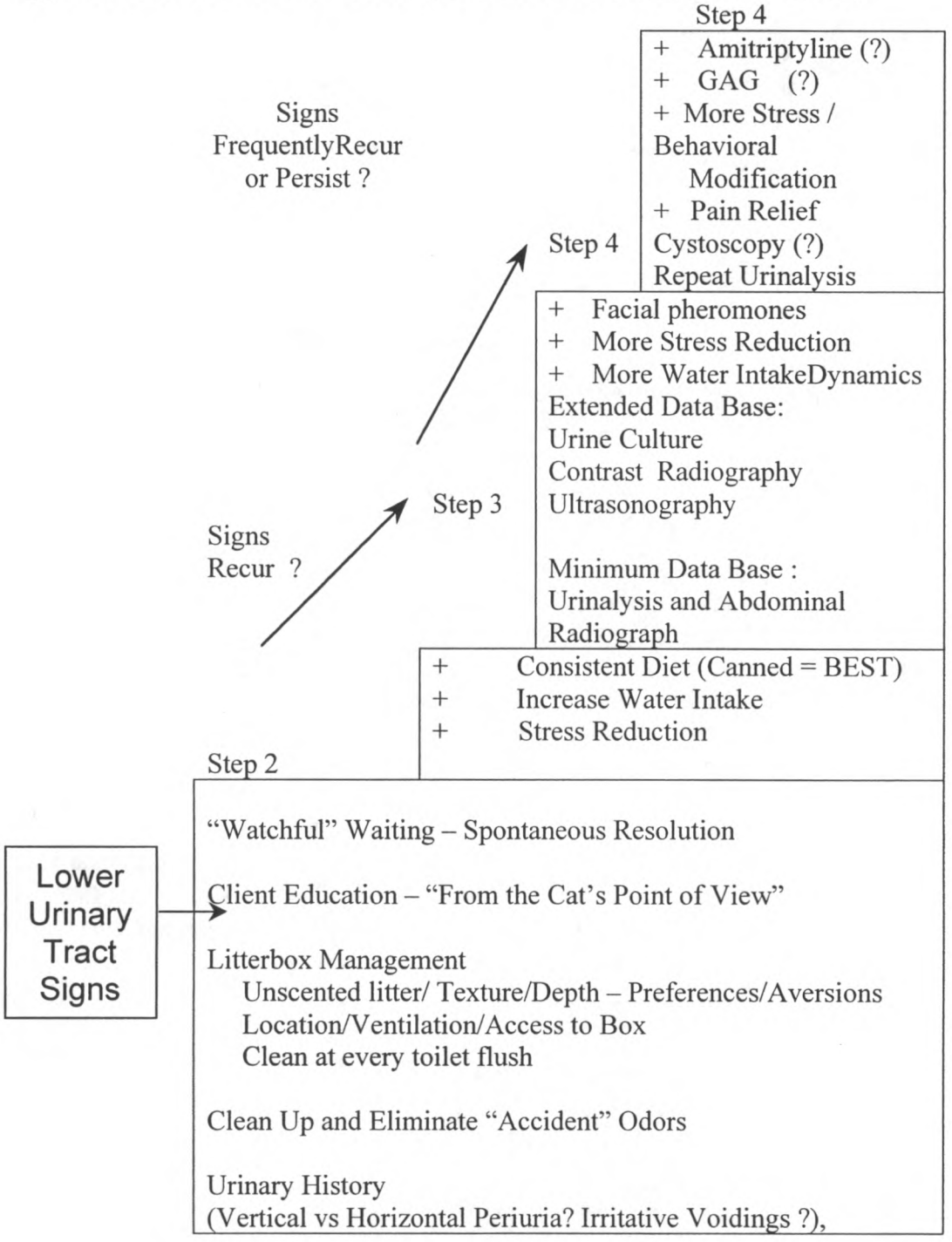


Figure 2C . Contrast radiography is indicated in cats with recurrent or persistent clincal signs in which no abnormalities were seen on plain radiographs. Small stones, anatomical abnormalities (urethral stricture in males, urachal diverticulum) and mass-like lesions may be disclosed, although neoplasia of the cat bladder is very uncommon. Ultrasonography may show radiolucent cystic calculi and is useful for the assessment of bladder wall thickness if the bladder is at least moderately distended with urine. Ultrasonography is not useful for the evaluation of the urethra however. Urethrocystoscopy is useful to exlcude small urinary calculi and to evaluate the bladder and urethra for anatomical abnormalities. Additionally, cystoscopy provides the most information about mucosal detail – it is more likely to detect mucosal abnormalties with this method than with other imaging modalities. At present, it is necessary to see "glomerulations" following bladder distension to 80 cmH20 pressure in order to make the diagnosis of interstitial cystitis. Interstitial cystitis is a sub-category of idiopathic cystitis. The question mark between idiopathic and interstitial cystitis at the bottom indicates that it is not know how many cats with a diagnosis of idiopathic cystitis would have a diagnosis of interstitial cystitis if evaluated with a cystoscope.

Figure 3. What do WE Do ? Step-wise approach to treatment of cats with idiopathic lower urinary tract signs. More diagnostics should be performed when cats fail to spontaneously clear of their initial lower urinary tract signs and when signs recur to ensure that the diagnosis is really idiopathic lower urinary tract disease. Properly controlled clinical trials may provide better approaches to treatment in the future, but this is what we do in the interim.



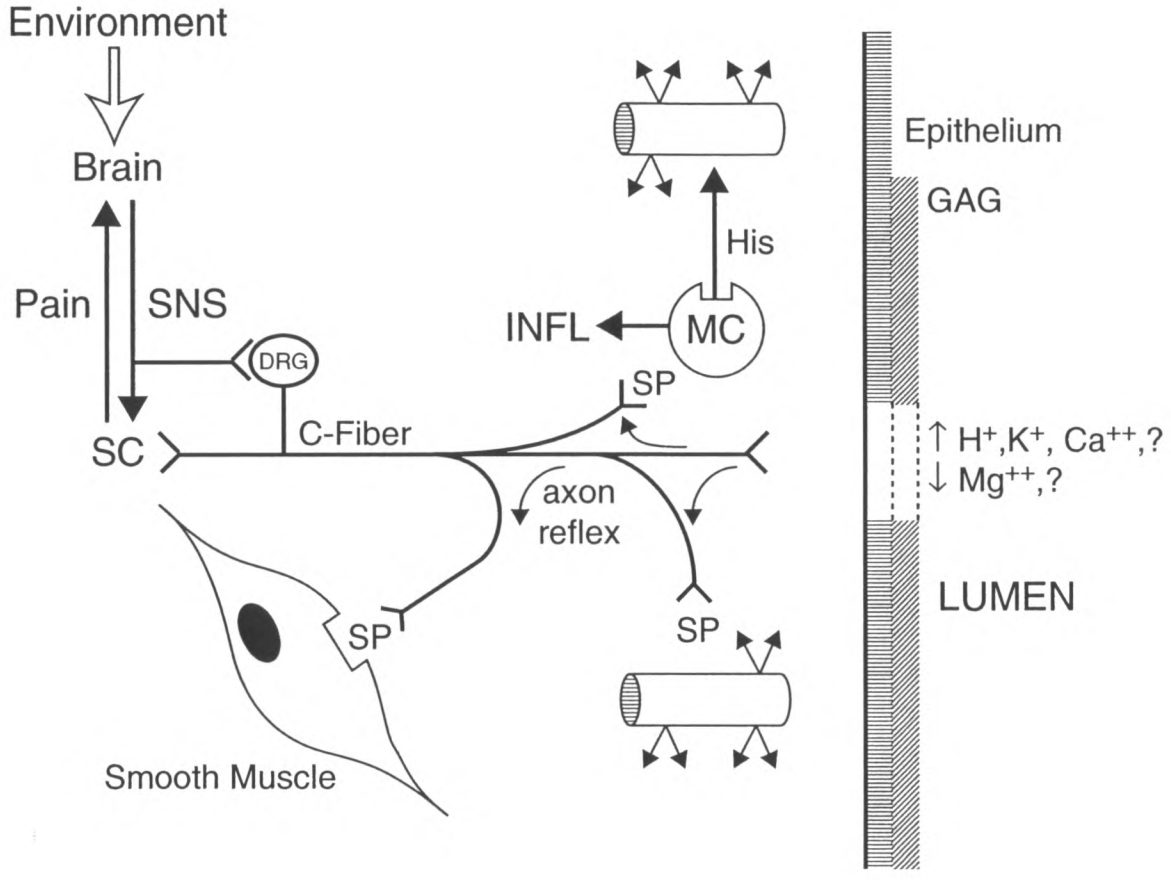


Figure 4. Neurogenic inflammation as it affects the urinary bladder.

Sensory neurons (C-Fiber) seem to play a central role in transmission of action potentials via the dorsal root ganglia (DRG). These signals are perceived as painful by the brain. Sensory fibers also can propagate a local axon reflex without transmission of an axon potential. The axon reflex results in release of peptide neurotransmitters such ass substance P (SP) by the nerve endings. Interaction of SP with receptors on vessel walls results in vascular leakage, that can be augmented by SP-induced release of histamine by mast cells. These actions may give rise to the submucosal petechial hemorrhages observed at cystoscopy. Receptors for SP also occur on smooth muscle, which when activated stimulate muscle contraction. Also shown are the urothelium (epithelium) and the overlying glycosaminoglycan (GAG) layer adjacent to the bladder lumen. Damage or malfunction of either or both of these layers may permit constituents of the urine, such as protons, potassium ions, or hyperosmolar (>2,000 mOsm/L) fluid to activate the sensory fibers. The effects of stress on sensory fibers may be related to descending efferent sympathetic (SNS) signals stimulating the DRG and inducing peripheral release of neuropeptides. Local release of neurotransmitters by bladder sympathetic fibers also could stimulate sensory fibers. Another factor probably involved in chronic bladder inflammation, but not shown, is local and systemic release of nerve growth factors, which may promote sensory fiber terminal sprouting to increase the size of sensory fiber receptive fields.

Updates on Feline Lower Urinary Tract Disease

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Animal Shelter Surrender

4 Million Cats per Year
Estimated
Patronek GJ, et al JAVMA 209:582-588, 1996

Most = Inappropriate Urinary Elimination

Epidemiology "FUS"

Incidence < 1%
Prevalence Rate 1%-6%

1.5% Prevalance Rate in 52 Private Practices
FUS or Cystitis
15,226 Cats
Lund EM et al: JAVMA 214(9):1336-1341, 1999

Epidemiology FLUTD – VMDB

Lekcharoensuk et al, JAVMA 218(9)2001
University Hospital Based
22,908 Cats with LUTD (1980-1997)

Proportional Morbidity Rate
= 8/100 Cats (all causes of LUTD)

2/100 to 13/100 by Institution

Epidemiology FLUTD - VMDB

Lekcharoensuk et al, JAVMA 218(9)2001
Idiopathic LUTD 63%
Urethral Obstruction 18%
Infections 12%
Urolithiasis or Plugs 10%
Urinary Incontinence 4%
Trauma 2%
Miscellaneous 2%
Congenital 0.7%
Iatrogenic 0.6%
Neoplasia 0.3%
Neurogenic 0.2%
Drugs and Chemicals 0.01%

Epidemiology Idiopathic FLUTD - VMDB
Lekcharoensuk et al, JAVMA 218(9), 2001
Increased Risk Male Castrated - OR 3.0
Decreased Risk Intact Female - OR 0.23

Increased Risk 4 to < 7 Yr - OR 2.6
Increased Risk 7 to <10 Yr- OR 2.6
Decreased Risk < 1 Yr- OR 0.12
No Increased Risk or Protection Detected by Breed

Risk Factors - Inappropriate Urinations
After Buffington 2001
INTERNAL
Genetic Factors
Experiential Background
Temperament

EXTERNAL
Complexity of Environment
Resource Quality/Availability
Sources of Threat/Conflict

Indoor Restriction for Cats
Common Veterinary Recommendation

Decreased Risk Infectious Diseases
Decreased Risk of Vehicular Trauma
Decreased Risk from Other Animals

Risk Factors - Indoor Restriction
LUT Signs

Odontoclastic Resorptive lesions

Obesity

Hyperthyroidism

Risk Factors - FUS
Excessive Body Weight
Decreased Activity
Indoor Litter Pans Exclusively
Living with Other Cats
Time Spent Indoors

Risk Factors - FUS (Jones New Zealand)
Time Spent Indoors - Dose Effect

Move to New House
Winter Months (Rainy Season)
Outdoor Prey Access = Protective

Environmental Factors
Benign
Challenging
Threatening
Provocative Environment ?

Internal Factors - Response to Environment
Minimal
Moderate
Severe

Sensitive Cat ?

Internal Factors - Response to Environment
Different Breed Susceptibility

Individual Temperament Differences

Magnitude of Response = Range is Large

Particular Individual + Environment
= Response Cannot be Predicted

Indoor Housing - Cats
MAY be More Sensitive to Effects
than Other More Social Animals (Dogs, Humans)
Cats = Relatively Solitary

< 50 / SQ Kilometer Hunting in Wild
Avoid Each Other During Hunting
Lieberg O, et al In :The Domestic Cat : the biology of its behaviour.

Two-Cat Household s
50% Time = Out of Each Other's Sight
Most Often Within 1-3 Meters of Each Other
Barry KJ et al: Applied Animal Behavior Science 64:193-211, 1999

Stressors for Cats ?
Indoor Restriction
Dry Foods
Altered Feeding Schedules
Unfamiliar Care Takers

Stress and Cats
Unpredictable Environment
Severe and Persistent

Hypothalamac-Pituitary-Adrenal Axis
Activation

Pontine Locus Coeruleus-Norepinephrine Activation

Signals from Environment
Pheromonal
Olfactory
Gustatory
Auditory
Cutaneous
Visual

Environmental Factors
Stress Response
IF
Perception of Control is Reduced

Stressed Cats
Decreased Play Activity

Decreased Exploratory Activity

More Time Hiding

Environmental Enrichment
Recommended for Cats
If Indoor Housing Maintained

Chronic House Soiling

Environmental Enrichment
Access to Resources

Interactions with Owners

Reduction in Level of Conflict
Environmental Enrichment
Feeding
Individually/Quiet Location

Dry vs Canned ?
Choices

Simulated Predatory Behaviors

Cleaned Feeding Bowel

Environmental Enrichment
Water

Freshness
Taste
Movement
Container Shape
Cleaned Water Bowel

Environmental Enrichment
Litter Box
Number
Location
Cleanliness ?

Depth
Size
Hooded
Tented
Mechanical

Environmental Enrichment
Physical Environment

Climbing
Scratching
Hiding
Resting

Elevations

Environmental Enrichment
Play Activities

(Nocturnal ?)

Petting
Grooming
Lures
Laser Pointers
Toys (mimic prey)

Environmental Enrichment
Increase Access
to
Outdoors ??

Environmental Enrichment
Litter

Preference
Aversion
Depth
Slope
Clumping
Scent

Environmental Enrichment
Little to No Controlled Studies
Preliminary Studies Underway at OSU (Buffington 2001)

Alpha -2 Adrenoceptors
Alpha-2 AR Throughout Brain
Large Amount in LC
Most = Inhibitory Receptors

Presynaptic Stimulation
= Inhibits NA Release and Downregulates Outflow

GAG-Treatment ?
Uricon® - Pentosan Polysulfate
DVM Pharmaceuticals

Pending FDA Approval
Uricon® - PPS Treatment of IC
Multicenter, Double Blind
Placebo-Controlled, Prospective

Ohio State
Michigan State
Purdue
Tennessee

Treatment of FIC:GAG Replacers

Elmiron
(Pentosan Polysufonate Sodium)

Cosequin
(Glucosamine, Sodium Chondroitin Sulfate, mixed GAGs, Manganese)

CYSTAID ® - VetPlus UK

Treatment of Idiopathic Cystitis
What Do We Do ?
Clean Soiled Areas
Litterbox Dynamics
Stress ID and Reduction
Increase Water Intake
Pain Relief
Amitriptyline
GAG Replacers
Facial Pheromones

Litterbox Dynamics
Rule of "1 + 1"
Cleaning Schedule
No Scented
Clumping
Litter Texture
Depth of Litter
No Hoods
Location
Access

Possible Resource for Cleaning Soiled Areas
Urineplanet.com
Urine Deodorizer/Removal Kit

Idiopathic Cystitis
30 to 50% Recurrence within12 Months

85% Spontaneously Resolve Episode
5 to 7 Days (Many Earlier)

Pathophysiology of FIC ?
Noxious Urine
Leaky Bladder
Altered GAG Dynamics
Altered Urothelium
Neurogenic Inflammation
Mast Cell Infiltration
Increased Sensory Nerves
Increased Sympathetic Outflow

Idiopathic Cystitis and Diet

18 Canned & 28 Dry

0 Recurrence over 1 Year
16/18 Canned (89%)
17/28 Dry (61%)

10% Recurrence on Canned
40 % Recurrence on Dry

60% Helped by Constancy of Dry Diet
30% More Helped by Canned Diet
10% Not Helped by Diet

Idiopathic Cystitis and Diet
Acid Urine = No Known Benefit
Harm ?

Crystalluria = No Known Detriment

Mg Restriction = No Known Benefit
Harm ?

Diet and LUTD - Cats
Idiopathic Cystitis
Stone-Formers

IF Possible, Never Eat Food Dry
Idiopathic Cystitis and Stone-Former Cats
Identified Themselves as Predisposed
to these Conditions

Sensitive Cats
in a Provocative Environment

Increasing Water Intake
Canned Food
Water to Dry Food
Fresh Water
Water Bowl Filling Dynamics
Bottled Water
Running Water
Flavored Water

Stress Reduction
More Cat-Like Activities
Hunting/Climbing
More Quality Time with Cat
Decrease Numbers of Cats in House
Decrease Stress of Owners

Some Cats Don't Belong
with Some People

Drugs and Idiopathic Cystitis
NOT Before Excellent Workup
NOT Before Client Education
Litterbox Dynamics
Stress Reduction
Water Dynamics

Recurrent/Persistent Cases Only

Drugs and Chronic/Recurrent Idiopathic Cystitis
Amitriptyline
Other Norepinephrine/Serotonin Reuptake Inhibitors ?

Analgesics

Glycosaminoglycans ?
Feline Facial Pheromones ?

Treatment of FIC:
Stress management
Feliway
Facial pheromones
May have a calming effect if sprayed in the cat's environment

Treatment of FIC:Pain Management
Butorphanol can be used
0.1 mg/kg IV
0.4 mg/kg SQ
Fentanyl patches also can be considered in severe cases

FIC = A "Sensitive" Cat in a "Provocative" Environment

IC – CNS Changes
Treatment - Cats
Environment
Ingestion
Elimination
Interaction

Resources for Owners of Indoor Cats
From the Cat's Point of View
www.perfectpaws.com

Felinestein

MANAGEMENT OF MALE CATS WITH URETHRAL OBSTRUCTION

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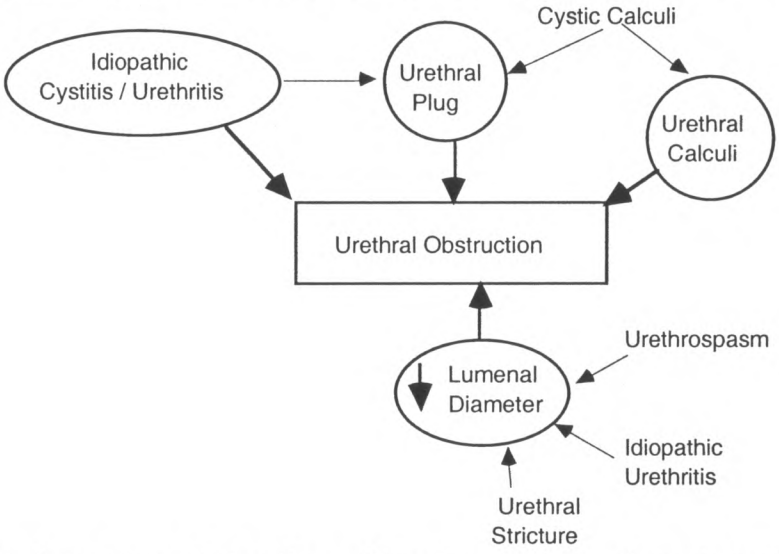
Pathophysiology of Urethral Obstruction

Urethral plugs are the most common cause of obstruction in male cats. In one series (Krueger 1991), urethral plugs occurred in 60%, no cause was found in 30%, uroliths alone were documented in 10% (struvite exclusively) and uroliths with bacterial urinary tract infection were observed in 2%. Occasionally stricture and rarely neoplasia are the causes of obstruction. Urethral obstruction due to calcium oxalate urethroliths is a phenomenon of the 1990's that was not encountered in the 1980's.

Figure 1) UNDERLYING CAUSES AND MECHANISMS OF URETHRAL OBSTRUCTION



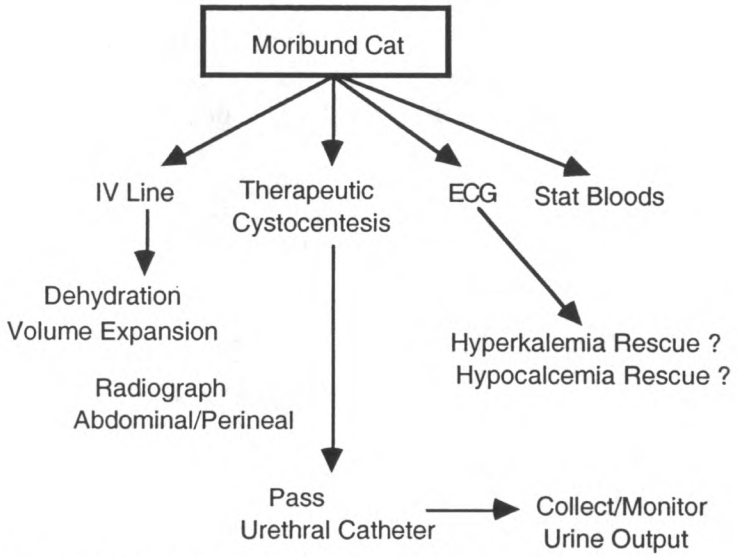
Most plugs cause obstruction within the penile urethra, but obstructions can also occur at more proximal sites. The predominant mineral composition in most plugs is magnesium ammonium phosphate (struvite). Secondary components can contribute to plug formation including inflammatory exudate (WBC and proteins), red blood cells, cellular debris, sloughed tissue (epithelial cells), struvite crystals and combinations. Virus-like particles resembling calicivirus and bacteria have also been observed within urethral plugs examined by transmission electron microscopy. Primary inflammatory changes (exudates, blood, and edema) or changes within the urethral wall secondary to intraluminal urethral plugs may contribute to the obstructive process. These changes may be magnified following instrumentation with catheters and back-flushing solutions used in therapeutic endeavors.

Diagnostics and Management

Urethral obstruction is diagnosed by the finding of an enlarged bladder in a male cat with signs of urinary urgency, difficulty in manually expressing urine, and by resistance encountered during the passage of a urethral catheter. It may not be obvious what is causing the urethral obstruction. Diagnostics and management of urethral obstruction are performed simultaneously. The degree of uremia, electrocardiographic stability, and the magnitude of bladder distension will dictate how

quickly and in what order treatment must be performed. Those cats with uremic crisis and those with very large hard bladders are in need of prompt attention.

Figure 2). APPROACH TO THE MORIBUND CAT WITH ADVANCED URETHRAL OBSTRUCTION



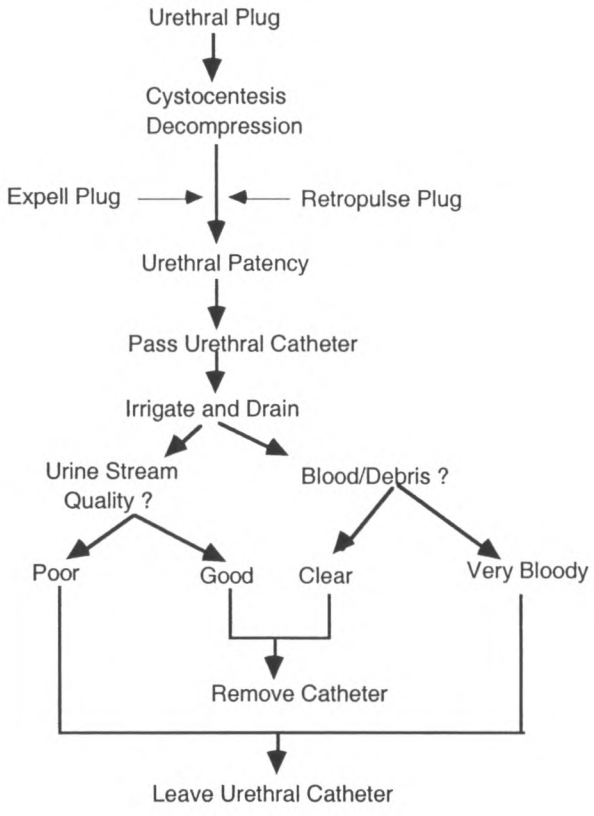
Relief of Obstruction Due to Plugs

Cystocentesis to drain the bladder(decompressive or therapeutic cystocentesis) should be performed as soon as possible in cats with very large bladders to prevent rupture of the bladder and to allow excretory renal function to resume. Relief of bladder pressure prior to urethral catheterization also may facilitate efforts to dislodge urethral plugs, and provides a superior urine sample for analysis prior to manipulation of the urinary tract and contamination with flushing solutions. Plain abdominal/perineal radiographs should follow the decompressive cystocentesis so mineralized plugs can be documented or that cystic and/or urethral calculi can be identified (a lateral radiograph often suffices).

Chemical restraint/anesthesia (isoflurane, low-dose IV ketamine, propofol) is often advisable to atraumatically relieve the obstruction via urethral catheterization. Urethral relaxation while under sedation/anesthesia may further increase the likelihood of plug dislodgment. Little or no sedation is indicated for those with severe uremia. Gentle massage of the penis may dislodge a urethral plug located in the penile urethra, especially when near the external urethral orifice. Gentle pulsatile bladder palpation following penile massage may cause a plug to be expelled. Rectal massage of the pelvic urethra may on occasion also contribute to plug dislodgment. Aseptic and gentle technique should be used while placing a urethral catheter. Urethral irrigation with sterile physiologic solutions (Lactated Ringer's solution or 0.9% saline) may now dilate the urethra and flush the obstructing plug distally out the external urethral opening around the catheter. Intermittent gentle digital pressure on the bladder following irrigation attempts may change the pressure on the urethral plug and force it to be expelled through the external urethral orifice. Care must be taken to ensure that excessive trauma or rupture of the bladder does not occur during this maneuver. Hydropulsion (reverse flushing) within the urethra may be

attempted at this point if the obstruction is not yet relieved. The urethra is thoroughly flushed to make sure that all debris initially within the lumen has been back-flushed into the bladder or has been refluxed out the urethra. The urethral catheter can then usually be advanced into the bladder. Failure to adequately remove debris from the bladder and urethra is a major cause of rapid re-obstruction following catheter removal.

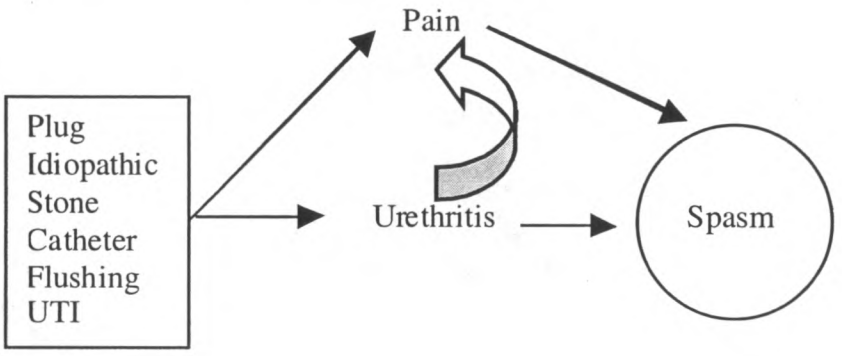
Figure 3). A Potential Decision-Making Algorithm - An Approach to Management of Urethral Obstruction in a Male Cat Due to a Urethral Plug



"Urethral spasm" refers to pathologic neurogenic or myogenic processes that contract the circular smooth and/or skeletal muscle of the urethra. The bladder and preprostatic segments of the urethra contain primarily smooth muscle, the prostatic and postprostatic segments contain both smooth and skeletal muscle, and the musculature of penile segment is predominantly circular skeletal muscle. Innervation of the urethra is provided by the sympathetic nervous system via the hypogastric nerve and the somatic nervous system via the pudendal nerve. Part of urethral tone maintained by the skeletal muscle (rhabdosphincter) is influenced by sympathetic innervation.

Stimulation of adrenoreceptors (particularly a-1) within the urethra increases urethral tone in normal cats. It is likely that both pain and stress associated with urethral obstruction increases

sympathetic outflow from the central nervous system, favoring urethral spasm. Urethritis may exist prior to plug formation, or may be acquired secondary to trauma from the physical presence of intraluminal plugs or stones. Attempts to relieve obstruction with catheters, and indwelling urethral catheters also can result in urethritis. Urethritis may also be secondary to bacterial urinary tract infection (UTI) that is commonly acquired following placement of indwelling urinary catheters, even when a closed urinary collection system is employed. The use of antibacterial treatment does not prevent UTI.



To reduce pain and inflammation associated with intraluminal obstructing material, all material must be removed from the urethra. Using gentle technique during urethral catheterization and flushing is essential to minimize iatrogenic damage to the urethra (erosion, inflammation, perforation). Installation of an indwelling urethral catheter can be an additional source of pain and urethritis, which should be avoided if possible. Repeated cystocentesis to empty the bladder is an alternative to passage of another urethral catheter if obstruction recurs following removal of the initial catheter. Repeated cystocentesis also provides indirect pain relief by keeping the bladder small and painful mucosal surfaces non-distended.

Drugs recommended for the treatment of urethrospasm include analgesic, anti-inflammatory, antibacterial, and spasmolytic agents. Injection of diluted lidocaine solution through the urethral catheter at the time of its removal has been advocated by some to reduce urethral spasms, but this has not been critically evaluated. Also, the local effects of lidocaine on urothelial healing are unknown. If used, lidocaine should be diluted and injected slowly at low pressure – excessive amounts of systemically absorbed (> 0.5 mg/kg IV) lidocaine can cause seizures. Systemic treatment with a fentanyl (patch), low dose morphine (0.05-0.2 mg/kg IM), butorphanol (0.05-0.2 mg/kg IM), and/or low dose medetomidine (2-5 micrograms/kg IM ; centrally acting alpha-2 agonist that decreases sympathetic outflow) for relief of pain seems reasonable. It is possible that relief of pain will decrease urethral and bladder muscle spasms. Opioids increase urethral sphincter tone, increase bladder volume, and inhibit voiding initially but tolerance to these effects develops quickly. The central analgesic effects of opioids are most important. Butorphanol is a weak opioid that can be considered for use during the initial 12-24 hours. Unfortunately, patients develop tolerance to butorphanol rapidly. Butorphanol also has a ceiling effect in which increased doses provide no further analgesia. Finally, butorphanol produces agonist effects at kappa receptors and antagonist effects at mu receptors. This may decrease the effects of more potent mu opiods (morphine, oxymorphone, fentanyl) when needed. When additional analgesia is needed, combinations of drugs that act by different mechanisms should be considered. For example, morphine (opioid) and medetomidine (alpha 2 agonist) may be given every 6 to 12

hours as needed. Ketoprofen, tolfenamic acid, and carprofen are non-steroidal anti-inflammatory drugs (NSAID) that have been used in cats, but their effectiveness in decreasing lower urinary tract inflammation has not been substantiated. Adding an NSAID to this regimen might provide the most complete level of analgesia.

Oral prednisolone failed to reduce urethral histopathology in cats that underwent indwelling urethral catheterization for 3 days (Barsanti1992). Glucocorticosteroids should not be given to cats while an indwelling urethral catheter is in place due to the associated high risks for development of bacterial pyelonephritis. Whether this risk is still present if glucocorticosteroid treatment is given at the time of catheter removal is not known.

Spasmolytic therapy may need to be directed against increased tone of both smooth and skeletal muscle. Phenoxybenzamine, acepromazine, and prazosin are alpha-adrenergic antagonists that decrease smooth muscle urethral tone in healthy cats. Caution must be practiced when administering adrenergic antagonists, since the adrenoreceptor profile along the urethra may change in disease states compared to normal cats. Additionally, the effects of such agents may vary depending on whether the predominant actions are central or peripheral. Flavoxate and oxybutynin exert a direct action to reduce smooth muscle tone. Diazepam reduces skeletal muscle tone to the urethra through a central mechanism, while dantrolene exerts its effect on skeletal muscle directly. Prazosin and dantrolene have been shown to decrease urethral tone in male cats following relief of urethral obstruction.

Chronically, treatment is aimed at controlling the underlying inflammatory condition (idiopathic cystitis/urethritis). Efforts to decrease stress in the cat's life and to increase water turnover are indicated for those with idiopathic cystitis. Increased water intake to reduce urine specific gravity and specific diet changes are indicated for cats with struvite or oxalate urolithiasis. Cats that have previously formed a urethral plug containing struvite as the major mineral constituent should eat foods that promote a urinary pH from 6.2-6.5 to ensure maximal solubility of struvite while avoiding overacidification.

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Feline Urolithiasis

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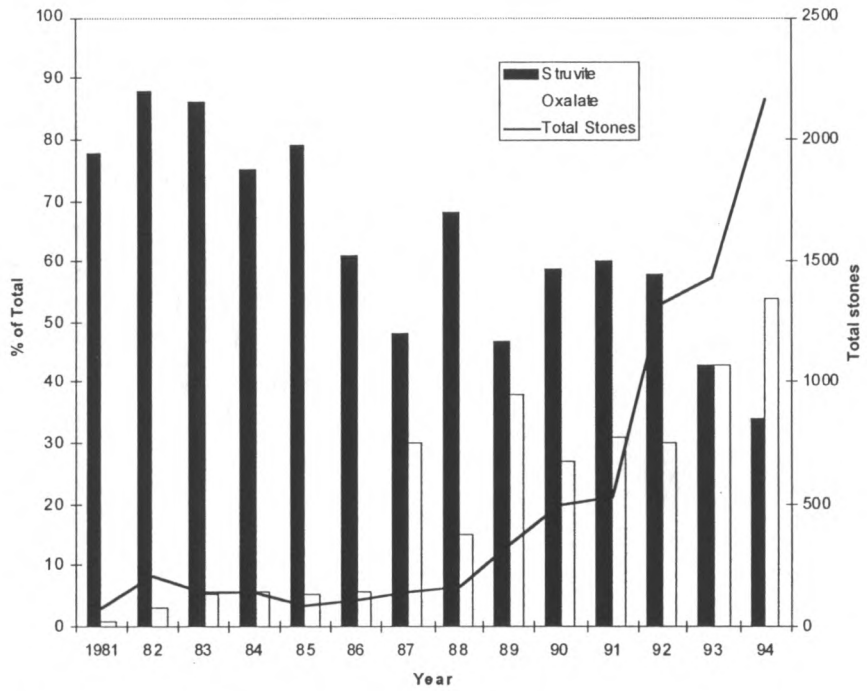
The two most common stone types in cats are struvite and calcium oxalate. Prior to the late 1980s, sterile struvite was the most common urolith found in cats. The proportion of struvite urolithiasis declined in subsequent years following changes in commercial cat food formulations. Unfortunately, this decline appears to have come at the expense of an increase in the proportion of calcium oxalate uroliths. The proportion of stones analyzed at the University of Minnesota Urolithiasis Center has shifted from approximately 65% struvite and 2% calcium oxalate in 1984 to 48% struvite and 40% calcium oxalate in 1995.

Cat urinary bladder stones analyzed by the University of Minnesota Urolith Center between 1981 and 1994. The solid line represents the total number of stones. The black bars represent the



proportion of total stones that were struvite, while the open bars represent the proportion of calcium oxalate stones.

Struvite Urolithiasis

Struvite crystalluria is not synonymous with struvite urolithiaisis; struvite urolithiasis can occur with or without struvite crystalluria, and struvite crystalluria can occur in apparently normal cats. Unlike dogs, the vast majority of cats form struvite uroltihs in sterile urine. Struvite (magnesium ammonium phosphate) urolithiasis and urethral obstruction have been induced experimentally in healthy cats by feeding diets containing three to ten times the amount of

magnesium found in commercial cat foods. These studies led to the conclusion that magnesium was a primary cause of naturally occurring struvite urolithiasis in cats. It subsequently was learned that struvite stones in the bladder of healthy cats fed large quantities of magnesium dissolved when the urine pH was reduced to approximately 6. These results suggested that magnesium's effect on struvite formation depended on the urine pH. This idea was supported when it was found that the form of magnesium used in previous studies increased the urine pH. The research implicating magnesium as a potential cause of urinary stone disease in cats seems to have led cat food manufacturers to restrict the magnesium contents of diets, and to add ingredients to promote a more acidic urine in an attempt to minimize the struvite-promoting potential of their products. In retrospect, it appears that few client-owned cats formed struvite urolithiasis despite consumption of commercial foods that were alkalinizng and magnesium-replete. This suggests that these diets unmasked cats intrinsically susceptible to struvite stone formation rather than directly causing stone formation.

The presence or absence of struvite crystalluria on a random urinalysis does not predict which cat will form a stone for the first time, though the persistence of struvite crystalluria is a risk factor for recurrence of struvite urolithiasis. We have observed the formation of naturally occurring struvite urolithiasis in cats consuming dry diets designed to inhibit struvite formation. This observation emphasizes the significance of that most important nutrient, water, in the treatment of cats with all types of urolithiasis.

Medical dissolution of struvite urolithiasis using dietary methods has been reported. In an uncontrolled study, consumption of a *canned*, magnesium-restricted, urine acidifying, salt-supplemented diet dissolved naturally occurring struvite calculi over several weeks in cats. Although magnesium-restricted acidifying diets are commonly employed to prevent recurrence of sterile struvite uroltihiasis in cats, no data exists to prove their effectiveness in doing so. Because so many commercial American diets for cats have been modified to restrict the formation of struvite, clinicians should recognize that acidifying agents such as ammonium chloride or d,l-methionine no longer are needed to maintain acidic urine in cats consuming these foods. Acidifying agents should not be routinely prescribed for cats with struvite urolithiasis because they impose an additional source of acid that may contribute to the development of metabolic acidosis.

Calcium Oxalate Urolithiasis

Calcium oxalate crystalluria is not synonymous with calcium oxalate urolithiasis; oxalate crystalluria occurs in some apparently normal cats, and oxalate urolithiasis can form with or without oxalate crystalluria seen on urinalysis. Only about half the cats of one report with calcium oxalate uroliths had calcium oxalate crystalluria at the time of diagnosis, and 9% had struvite crystalluria.

In contrast to struvite stone formation, experimental diet manipulations that induce calcium oxalate stone formation in healthy cats have not been reported. Acidifying diets increase both urine concentration and fractional excretion of calcium, and magnesium restriction reduces the urine content of magnesium. These circumstances appear to increase the risk of calcium oxalate formation. Previous commercial cat diets that did not restrict magnesium or reduce urine pH may have obscured

this susceptibility by resulting in formation of urine in which calcium oxalate stones were unlikely to form. When cat food manufacturers added acid-forming ingredients and reduced the magnesium content of foods to prevent struvite formation, the diets may no longer have protected cats prone to calcium oxalate formation. Cats susceptible to calcium oxalate formation were now consuming a "provocative" diet. The diet modifications made by cat food manufacturers may not have "caused" an increase in calcium oxalate urolithiasis, however, but only have exposed a population of cats already genetically predisposed to calcium oxalate formation (diet sensitive rather than diet induced). This hypothesis is compelling in cats, because the overall occurrence of calcium oxalate urolithiasis in the United States appears to be no greater in cats than it is in humans, despite the fact that much of the cat population consumes similarly formulated diets.

Two studies of epidemiological factors associated with the development of calcium oxalate urolithiasis in cats recently have been published. In a study comparing 91 cats with calcium oxalate urolithiasis with 258 age and sex matched controls, increased risk was associated with older age (bimodal peaks at 5 and 12 years), Persian and Himalayan breed, indoor housing, and consumption of urine acidifying diets[Kirk, 1995]. The other study reviewed the records of 3,498 urolith accessions between 1982 and 1992[Thumchai, 1996]. This study too found increased risk in older cats, Persian and Himalayan (and Burmese) breeds, and that stones removed from the kidneys were more likely to be calcium oxalate than struvite. Males and females appear to be at equal risk; male dogs are at greater risk than females for calcium oxalate urolithiasis. Both studies were based on samples of convenience, however, so these results may not represent the general population of cats.

Hypercalcemia and calcium oxalate stone formation occasionally occurs in cats with primary hyperparathyroidism. Veterinary urologists from the University of Minnesota Urolithiasis Center recently reported idiopathic hypercalcemia to be present in approximately one-third of cats from which calcium oxalate stones had been removed and submitted to them for analysis. Similar findings also were reported from the University of Georgia.

No medical regimen has been shown to successfully dissolve calcium oxalate uroliths, so surgery or voiding urohydropropulsion is recommended for these patients. To prevent recurrence, some stone-specific alterations may be useful in addition to dilution of the urine. Although a decreased risk of recurrence of oxalate stones related to diet change has never been documented in cats, changing to a diet that is less acidifying and that has not been magnesium-restricted seems reasonable, as long as the resulting urine specific gravity is ~1.020. Acidifying agents are contraindicated in cats with calcium oxalate urolithiasis. Some veterinary food manufacturers offer diets designed to reduce the probability of calcium oxalate stone formation. These diets have been tested in healthy cats, and it is hoped that they will prove effective in cats with naturally occurring stone disease. The frequency of recurrent calcium oxalate stone formation in cats is not known, so the safety, efficacy, and cost-effectiveness of these diets cannot yet be determined.

Treatment of Urolithiasis – General

The frequency of urolithiasis does not appear to be greater in cats than in either dogs or human beings, so no modification of the diet is necessary prior to formation of the first stone. Treatment of sporadic calcium oxalate or struvite crystalluria is not necessary in cats that have never

formed a stone previously; neither oxalate or struvite crystalluria (without stone formation) is know to damage the urothelium[Cohen, 1991]. Therapy of cats with a stone includes acute treatment to remove or dissolve the stone, and chronic therapy to reduce the risk of recurrence. Stone-specific treatment recommendations can be based on quantitative stone analysis when stone material from spontaneous voiding, catheter aspiration, voiding urohydroexpulsion or surgery can be obtained for analysis. When the stone type is unknown, the choice of empiric medical or surgical therapy is offered to the client after the risks and benefits have been explained.

Post-operative abdominal radiographs should be taken to ensure that all calculi were removed, otherwise "pseudo-recurrence" of urolithiasis may occur. Failure to remove all stones at the time of cystotomy is common (20% of cats in one study [Lulich, 1993]) and seems to be more likely to occur with calcium oxalate uroliths. Flushing of stones from the bladder to the urethra as well as dragging stones distally during urinary catheter withdrawal are suspected procedures that could account for this.

All cats that have formed a stone are at increased risk for recurrence. Urolithiasis seems to be a diet sensitive disease, in which an intrinsic susceptibility in the patient is exposed by provocative nutrients. Water may be the most important nutrient to prevent recurrence of stone formation. Increased water intake is the cornerstone of therapy for urolithiasis in both human and veterinary medicine. Increasing water intake to dilute urine and increase frequency of urination is an important part of treatment. Decreasing the concentration of potential stone-forming minerals in their urine and increasing their voiding frequency are primary therapy to reduce the risk of formation of a new stone. When a urolith is diagnosed, the patient should be switched to a canned diet, or water (one cup per cup dry food) should be added to the dry food before presentation to the cat. Additional water can be added to the food to reduce the urine specific gravity until food intake declines; the goal of a urinary specific gravity near 1.020 is recommended. A food appropriate for the stone type should be chosen if possible. Salting the food or water is not recommended for cats with calcium oxalates as the extra sodium may increase calciuria.

In those cats with a history of both struvite and calcium oxalate urolithiasis, prevention regimens should be biased toward calcium oxalate since we can successfully dissolve the struvite but not the oxalate stone with medical dissolution protocols if needed.

Struvite and Calcium Oxalate Urolithiasis in Cats - Diagnosis, Treatment and Prophylaxis

Dennis J. Chew, DVM
Dip ACVIM

Uolithiasis - Settings

No Clinical Signs
- Fortuitous
- Evaluation of Previous Stone-Former

Cystitis Without Obstruction
- Sterile/Infected

Obstructive
- Sterile/Infected

Urolithiasis

Stone Type Frequency Has Dramatically Changed

Struvite(MgNH4P04)

Calcium Oxalate

Urates

Cystine

Change in Stone Type ?

"The War on Urolithiaisis"
Dr. Carl Osborne

Battle # 1 : Struvite = Victorious

Battle# 2 : Calcium Oxalate = Still Ongoing

Urolithiais - Data Base

Urinalysis
Urine Culture

Urinary Tract Imaging

Stone Analysis - QUANTITATIVE

Stone Type Profiling - Guesstimate

Species

Sex

High Risk Breed

Stone Type Profiling - Guesstimate

Location

Radiodensity (Ox > MAP)

Size
- MAP = larger ; Oxalates = smaller

Shape of Stone
- Smooth/Jagged
- Wafer

Stone Type Profiling - Guesstimate

Urine pH

Crystalluria

UTI

Diet

Radiographic Density - Uroliths

High ↓ Low

- Oxalate
- Calcium Phosphate
- Silicate
- Struvite
- Urate
- Cystine

Urolithiasis - Data Base Imaging- Lower Tract

Plain Abdominal Radiographs
Contrast Urethrogram
Contrast Cystogram
Intravenous Pyelogram (IVP)
Ultrasound

Surgical Inspection

Endoscopy

Survey Radiographs

Is a Lateral View Alone = OK ?
Many Times = Yes

IF 2nd View = Avoid the VD and
Take an OBLIQUE
Avoids Overlying Pelvis

Contrast Urography

Pneumocystogram = Not Very Sensitive

Positive-Contrast
Ruptures, Urachal Diverticulae,
Urethral Lesions
Not Good for Mural Lesions or Uroliths

Double-Contrast = BEST

Try to Remove Small Stones at End -
Catheter Aspiration.

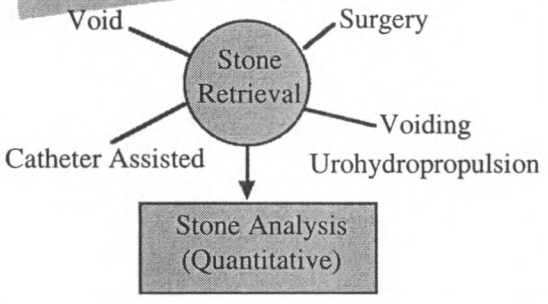
Calculi - General Rx

Induce Polyuria
⇓ USG
< 1.025

⇑ Voiding Opportunities

Treat Urinary Tract Infections

Stone Rx Approach



Stone Analysis

DON'T Submit Stones
in Formalin

Ruins Analysis

Stone Rx Approach - General

Retrieve Stone → Analyze Stone

Incomplete Stone Evacuation	Complete Stone Evacuation
↓	↓
Calculolytic Protocol	Prophylactic Protocol

Voiding Urohydropropulsion

Dr. Lulich Method

Non-Surgical Method
for Stone Removal

Small Stones
Females
Dogs and Cats

Voiding Urohydropropulsion

May Be Superior to Surgery
in Removal of Multiple
Small Calculi

Can Be Frustrating to Surgeons

Voiding Urohydropropulsion

General Anesthesia - Light

May Get Assist
from Detrusor Reflex

Catheterize Bladder
Fill to Moderate Distension
Hold Spine Vertical to Table

Voiding Urohydropropulsion

Agitate Bladder
Palpate Bladder - Gradually › Pressure
Urine is Expelled

Collect Stones

Count Stones - Compare to
Radiographs

Largest Stones Removed -VU
(Lulich)

Female Dog = 7 mm
Male Dog = 5 mm

Female Cat = 5 mm
Male Cat = 1 mm

Time = 7 - 45 Minutes

VU - Complete Removal 15/21
(Lulich)

9/11 dogs
5/7 females
4/4 males

6/10 Cats
5/8 Females
1/2 Males

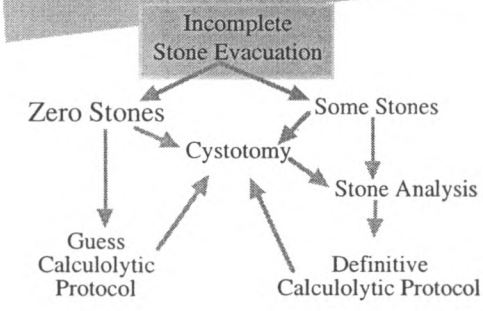
Modifications of Method (OSU)

Deep Anesthesia May Allow More
Urine/Stone Evacuation

⇑ Diameter of Urinary Stream
More Forceful Flow

Urethral Dilators
Cystoscopy

Voiding Urohydropropulsion



Stones Left Behind ?

Following Cystotomy
(Lulich)

14 % in Dogs (N= 57)

20 % in Cats (N=20)

Very Common Especially with Calcium Oxalates

Why are So Many Stones Left Behind ?

Flushing from Bladder to Urethra = Suspected

Dragging Stones Distally During Cathter Withdraw

STRONGLY SUGGEST = Flush ONLY
FROM Urethra to Bladder
Put Catheter in Tip of Urethra
Flush Vigorously

Struvite Urolithiasis

$MgNH_4PO_4.6H_2O$

Most Common Type
Both Dogs and Cats

Decreasing Frequency

Struvite Uolithiasis - Cats

90 % = Sterile
10 % = Infection-Associated

Dogs = 90-95% Infection - Associated

Struvite Uolithiasis - Cats

Wafer-Shaped/Discoid = Common
Often 1 Stone

When Many Stones = ⇑ Chances for UTI - Associated MAP

Struvite Urolith - Cat Profile

Thumchai JAVMA 1996

Breed

Non-Purebreds at Increased Risk

Persian, Himalayan, Burmese, and Siamese = ⇓ Risk

Age

1-2 Year Old at Greatest Risk

Sex

Neutered Females

⇓ Risk for Neutered Males

Struvite Urolithiasis

Bladder = Most Common Site

Dogs = UTI Most Important

Cats = Urine is Often Sterile

Urinary pH = Alkaline Urine

Struvite - UTI

Urease-Positive Bacteria

Staphylococcus
Proteus

Hydrolysis of Urea

Ammonia and Carbon Dioxide

Struvite Urolithiais - Genesis

During Progressive Alkalinity

$H_2PO_4^-$ → $HPO_4^{=}$ → $PO_4^{\equiv}$

⇓ Struvite Stones Analyzed Why ??

Less Stones Forming
- Diet Modification
- Better Control of UTI (dogs)

Less Stones Available for Analysis
- Medical Calculolytic Protocols = Successful

Struvite - Rx

Treat UTI = Primary

Keep Urine pH < 6.5

Calculolytic Diet

Urease Inhibitors ?

Calculolytic Diet-Struvite

Dogs

Very Low Protein

⇓ Ammonia

⇓ Magnesium

⇓ Phosphorus

⇑ NaCl

Cats = Not Protein-Restricted

Calculolytic Diet-Struvite

1 - 3 Months to Dissolve

Maintain 1 Month After Radiographic Dissolution

Struvite Dissolution - Cats

Dilute the Urine
- add water / ⇑ NaCl

Acidify Urine

⇓ Dietary Minerals - Precursors

Restrict Protein ?
Can't Restrict Enough in Cats

Sterile Struvite Dissolution - Cats

Sterile Struvite = Easy to Dissolve

36 Days Mean Dissoltuion

Infection-Associated Struvite Dissolution - Cats

Urease (-) UTI = 23 Days Mean

Urease (+) UTI = 79 Day Mean

Give Antibiotics Throughout

Struvite Stone-Dissolution

Cats = 3 Weeks If Sterile

Cats = 1.5 to 2.5 Months If UTI

Dogs = 2.5 - 3.5 Months for UTI-Associated

Struvite Stone- Prophylaxis

Maintain Urine pH 6.0 to 6.5

Increase Water Intake

Monitor for UTI Regularly if Infection-Related

Calcium Oxalate

Monohydrate
Dihydrate

Qualitative Analysis
= Frequent Non-Detection

Increasing Frequency

Calcium Oxalate Stones - Risk Faactors

Breed
Diet

Chronic Hypercalcemia
Hyperadrenocorticism

Risk Factors for Calcium Oxalates - Cats (Minnesota)

Urine pH < 6.3 - dry and canned foods
Dry Foods
% Dry Matter = ⇑ Risk if 49-60.5 %

⇑ Dietary Calcium (1.65-2.21 % DM) = Protective
⇑ Dietary Fat (33.1-41.4 % DM) = Protective
⇓ Dietary CHO (2.7-9.6 % DM) = Protective

⇓ Urinary Magnesium ? - Not Yet Studied

Calcium Oxalates and Hypercalemia - Cats

Approximately 1/3 = May Have or Develop Hypercalcemia (based on serum total calcium)

W/D ® Challenge = Restores Normocalemia in Many
Mechanism of Action = Unknown

Escape from Salutary W/D® Effect
= Happens in Some Cats After Months

Calcium Oxalate - Cat Profile

Thumchai JAVMA 1996

Breed
Persian, Himalayan, Burmese

Age
Increases with Age
Greatest in 10-15 Year Od

Sex
Neutered Male
Neutered Female at Decreased Risk

Diets and Acidification
USA - 1990's

Acidifying Ingredients High on List
Corn Gluten Meal
Digest

⇑ Acidifying Ingredients in Dry Food Compared to Canned

Calcium Oxalate Stone Formation

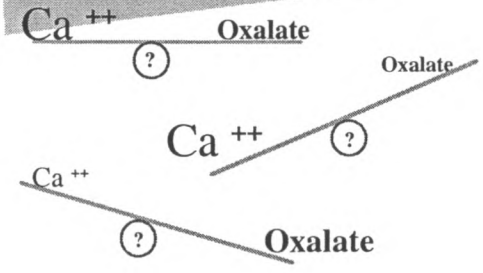
Calciuria

Oxaluria

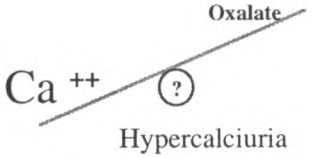
Crystal Promotor

⇓ Crystal Inhibitor

Calcium Oxalate Stone Formation - Theory



Calcium Oxalate Stone Formation - Theory



Hypercalciuria
=
Focus of Most Attention

Hypercalciuria -Resorptive

Acidifying Diets → Systemic Acidosis

Systemic Acidosis → Bone Buffering

Bone Buffering → Calcium Release

Calcium Release → ⇑ Renal Excretion (Calciuria) → Stone Formation ?

Increased Calcium Oxalate Urolithiasis

Acidifying Diet

Acidosis → Bone Buffering

Bone Buffering → ⇑ Ca^{++} - Serum

⇑ Ca^{++} - Urine + ⇓ Crystal Posion Action of ⇓ Mg

Mg- Restricted Diet → ⇓ Crystal Posion Action of ⇓ Mg

Calcium Oxalate Stone Formation

Hypercalciuria
Hyperoxaluria

⇓ Crystal Poison Activity
Hypomagnesuria
Hypocitraturia

Calcium Oxalate Stone Formation

⇑ Urinary Calcium (Oxalate)
+
⇓ Urinary Magnesium
+
⇓ Urinary Water

= High Risk Patient

Calcium Oxalate

Hypercalciuria

Hyperabsorptive

Resorptive

Renal Leak

Calcium Oxalate - Rx

Diet
Citrate
Vitamin B6
Thiazide Diuretics

Calcium Oxalate - Rx
Diet

Calcium
Oxalates
Sodium
Phosphorus
Citrates
Magnesium
Protein

Calcium Oxalate - Rx

Exclude Hypercalcemia

Urine pH = Not Important

Avoid Vitamin C
Diet = ?
Chlorothiazide
Potassium Citrate

Calcium Oxalate - Rx
Diet

⇑ Citrate
⇓ Protein
⇓ Sodium

⇓ Calcium
⇓ Oxalate

Calcium Oxalates - Regrowth

Slow Growing

3 - 4 Months to See on Radiographs

6 Months Until Large Enough
for Obstruction

Oxalate - Rx

Potassium Citrate

100 to 150 mg/kg per Day

Calcium Citrate =
More Soluble
than Calcium Oxalate

Calcium Oxalate Stones - Treatment

Medical Calculolytic Protocols
Do NOT WORK

Prophylactic Protocols
NONE Proven EFFECTIVE

Calcium Oxalate Stones - Dietary Prophylaxis

⇓ Calciuria / Oxaluria

⇓ Calcium Intake
⇓ Oxalate Intake

Protein Restriction
Mild Alkalinizing Diet

No Salt Supplementation
No Phosphorus Restriction
No Magnesium Restriction

Calcium Oxalates - ⇓ Recurrence

Canned Foods
Avoid Acidification

⇓ Protein (< 49% DM)
⇑ Calcium (> 1.6% DM)
⇑ Fat ((> 33% DM)
⇓ CHO (< 10 % DM)

Oxalates and Dietary Calcium

High Dietary Calcium = Protective

About-Face from Previous Reccs to
⇓ Dietary Calcium Intake

⇑ Dietary Calcium Intake =
⇑ Calcium Binding with Oxalates
= ⇑ Fecal Calcium Oxalate Excretion

Mild Alkalinizing Diet

Difficult to Find Off Grocery Shelf
Most = Acidifying

Canned Foods
= Less Acidifying in General

Veterinary Diets :
for Renal Failure Patients

Urologic Diets - "O" - Neutral U pH

Calcium Oxalate Stones - Dietary Prophylaxis

⇑ Water Intake

Add Water to Dry Food

Change to Canned Food

MOST IMPORTANT MANUEVER ?

Calcium Oxalates - Prevent Recurrences

Promote Water Intake
Canned Diets
Water to Dry

Urine pH > 6.5
Add Citrate If Needed

Calcium Oxalate Stones - Other Prophylaxis

Potassium Citrate

Thiazide Diuretics
Recurrent Cases Only

Calcium Oxalate Stones - Potassium Citrate

Citrate

Renal Excretion → Increased Urinary Citrate → Calcium Citrate (⇑ Solubility)

HCO_3 Generated → Mild Alkalinization → ⇓ Bone Calcium Resorption → ⇓ Calciuria

Oxalate - Rx

Potassium Citrate

100 to 150 mg/kg per Day

Calcium Citrate =
More Soluble
than Calcium Oxalate