

FELINE ATOPY – AN UPDATE

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Feline atopy is the most common hypersensitivity disorder seen in the cat, after flea bite hypersensitivity. In the older Veterinary literature, it has often been suggested that the incidence of atopy is similar to that of food sensitivity in the cat. However, in our clinic (predominantly a referral case-load), for cats showing the clinical signs listed below, about 80% are noted to be atopic and 15% food sensitive and 5%, a combination of both. Feline atopy is associated with a myriad of clinical signs. These clinical signs may be found alone or in combination.

1. Alopecia with or without dermatitis due to self trauma (may be a symmetric, self induced alopecia; higher prevalence areas tend to be the ventral abdomen, caudal thighs, dorsomedial forelimbs)
2. Pruritus directed at and restricted to the head and/or neck
3. Pruritic miliary dermatitis (lesions most commonly over the back, sides and head)
4. Eosinophilic plaques (pruritic) – most commonly over the medial thighs and ventral abdomen, but may be found over any area of the body
5. Indolent ulcer – upper lip; unilateral or bilateral.
6. Eosinophilic granuloma – variable pruritus; lesions may be found anywhere over the body; higher incidence in chin area (swollen chin, “pouty” chin; variable degrees of erosion/ulceration possible), caudal thighs (linear granuloma) and oral cavity (hard and soft palate).
7. Recurrent or persistent otitis externa; although usually bilateral, may be predominantly unilateral.
8. Pruritic dermatitis targeting the chin and perioral region; gives the impression of feline acne, but when area clipped, classic comedo formation is often not noted. However, if the patient does have concurrent feline acne, it would appear that atopic dermatitis in the chin area can worsen feline acne signs (i.e. increased comedones).
9. Rhinitis (sneezing) – uncommon
10. Conjunctivitis - uncommon
11. Asthma – arguments for this link between asthma and atopy include the fact that some individuals with experimentally induced disease have also been noted to develop skin disease. Affected cats had significantly more individual positive allergen reactions on both

intra-dermal testing and serum IgE testing than did unaffected cats. The efficacy of rush immunotherapy in an asthma experimental model has been noted. Responses to immunotherapy in naturally occurring cases have been noted but have been variable.

Affected individuals commonly have a peripheral eosinophilia and basophilia noted on CBC. Histologic examination of pruritus – induced and surrounding areas commonly show increased numbers of eosinophils and mast cells. Skin biopsy can be a valuable diagnostic aid to suggest that one is in the “camp” of allergic disease, but does not define the allergic disease (e.g. similar changes with atopy, food sensitivity, flea bite hypersensitivity, mosquito bite hypersensitivity).

Atopy is largely a diagnosis by rule out. Data from intradermal testing and/or in vitro serologic testing are definitely of value in establishing lists of allergens for purposes of hyposensitization, but because of the false positive and false negative associated with these testing technologies, neither should be used to DIAGNOSE atopy!

Secondary Bacterial Colonization / Infection

Secondary bacterial pyoderma occurs but appears to be less common than in the atopic dog, but remains an important consideration (underdiagnosed?). The bacteria most commonly incriminated are *Staphylococcus pseudintermedius* and *Staphylococcus aureus*, although other coagulase positive staphylococcal species (*S. schleferi coagulans*) and coagulase negative staphylococcal species (e.g. *S. epidermidis*, *S. schleferi schleferi*) may play an important role. These secondary infections may contribute significantly to inflammation and pruritus. They are best defined by cytologic examination and/or response to trial systemic antibiotic therapy. As a testament to the importance secondary bacterial infection can have with these atopy related lesions, a recent report of allergy related eosinophilic plaques documented a >70% reduction in plaque size with a 21 day Clavamox regimen (placebo therapy showed no benefit). The antibiotics most commonly used in the treatment of these secondary infections include Clavamox, cefovacin (injectable; every 2 weeks), cephalexin, cefpodoxine, cefadroxil, clindamycin (10 mg/kg q 24 hrs) or marbofloxacin (3 mg/kg q 24 hrs). We are now seeing a significant increase in the incidence of multi-drug resistant Staph. spp. in cats (usually methicillin resistant). Their presence is suggested by the finding of bacteria on cytologic examination, in the face of appropriate antibiotic therapy. Appropriate antimicrobial therapy is best suggested by culture and sensitivity testing.

Secondary Malassezia Colonization / Infection

Secondary Malassezia infections may contribute significantly to pruritus in atopic cats. In a recent report of 16 atopic cats with Malassezia overgrowth, Malassezia was most commonly noted on the face, ventral neck, abdomen and in the ear canals (in decreasing order of frequency) (Ordeix L et al, Vet Dermatology, 2007). The Malassezia-affected lesional areas were characterized by some degree of alopecia, erythema, greasy adherent brownish scales, increased cerumen, hyperpigmentation, easily plucked hair and follicular casts. Malassezia overgrowth was diagnosed by acetate tape stripping. A significant reduction in pruritus was noted in 5 of 7 affected cats who were treated with only azole therapy. The azole therapy most commonly used by the author to treat these secondary infections is itraconazole (5 mg/kg/day) or fluconazole (2.5 – 5.0 mg/kg/day).

General Therapy

1. The therapy of feline atopy should always include the documentation and treatment of secondary bacterial or Malassezia infections.
2. Topical Glucocorticoids:
 - a. Genesis spray (Virbac; .015% triamcinolone acetonide) has been used as an adjunctive therapy for “flares” of allergic dermatitis (e.g. twice daily for 1-3 days). Ingestion from licking the product has not appeared to be a problem, but this should be a concern for any longer term therapy. Emphasis is placed on treating infrequently. It is certainly possible that part of the benefit of this therapy is generated from the ingestion of the triamcinolone!
3. Tacrolimus: (0.1 %; Protopic; Fujisawa) – topical tacrolimus has been used to significantly reduce the dermatitis associated with atopy in the dog. It would appear to also be effective in cats, but as yet, the author is not aware of drug safety data that has been generated for the cat (specifically to assess the effects of drug that is ingested by licking at treated skin). Until this data is available, the author would recommend topical application only in those areas that cannot be licked (i.e. head). The product is used sparingly twice daily to initiate therapy.
4. Oral / Injectable Glucocorticoids: Because glucocorticoids are relatively well tolerated in the cat, they tend to be the cornerstone of therapy. However, as the disease becomes

more chronic and severe, it is not uncommon to have the patient require higher dosages, more frequent dosage administrations or more potent glucocorticoids to control clinical signs. It has been shown that prednisolone is more bioavailable and has improved drug kinetics when compared to prednisone in cats and therefore prednisolone is the oral glucocorticoid of choice in cats. Cats are often started on 1 – 2 mg/kg/day of prednisolone; goal for long term therapy is < 0.5 mg/kg every other day. Alternatively, methylprednisolone can be used to potentially reduce the incidence and severity of PU/PD (1.5 mg/kg/day to start). Oral triamcinolone may also be used effectively (starting at 0.2 mg/kg/day; goal for longer term therapy is < 0.08 mg/kg every other day). It has been suggested that fewer side effects may be associated with these dosages of triamcinolone than the dosages given for prednisolone. “Depo” steroids (e.g. methylprednisolone acetate at 4-5 mg/kg or 20 mg/cat or triamcinolone acetonide) are acceptable for periodic administration (ideally keep frequency of long term administration to less than once every 6-8 weeks). For very severe disease or patients refractory to prednisolone, consideration should be given to using the longer acting, more potent oral steroids at somewhat more aggressive dosages (oral dexamethasone starting at 0.3 - 0.4 mg/kg/day) or triamcinolone acetonide (0.2 – 0.4 mg/kg/day; maximum of 4 mg/cat/day). Emphasis should always be placed on reducing dosages to the least frequent administration possible (i.e. again, “goal” for prednisolone or methylprednisolone - < 0.5 mg/kg eod; for triamcinolone - < 0.08 mg/kg every other day). It has been suggested that transdermal preparations of prednisolone may be beneficial for some cats who refuse oral medication. These are generally cats that appear to respond to relatively lower dosages of prednisolone.

5. Fatty acids (omega 3 fatty acids are most commonly used for this purpose in the USA) benefit approximately 20 - 30% of cases (some quote 30 – 50%). Many cats, however, refuse to eat the fatty acids. Trial period is 3 months.
6. Antihistamines and Drugs with Antihistamine-like effects: The antihistamines that have been of most benefit in our hands for treating feline atopy are chlorpheniramine (2-4 mg/cat q 12 hrs), cetirizine (0.5 – 1 mg/kg or 5 mg/cat) or amitriptyline (2.5 – 5.0 mg/cat q 12 - 24 hrs). Amitriptyline may cause significant sedation, ataxia etc.; cats may salivate excessively when it is given. To minimize the chances of encountering sedation, the author starts at 2.5 mg total dose in the evening. If this is tolerated, 2.5mg is given in the AM and 2.5 mg in the PM. If this is tolerated, but is not beneficial in controlling the pruritus, the

dose is increased to 5 mg in the evening, 2.5 mg in the morning, then 5 mg BID if necessary. Problems with palatability can be circumvented by using amitriptyline powder mixed in fish/cod liver oil. Recent data regarding the efficacy of cetirizine show conflicting results (up to 40% of patients benefiting in one study, but only 5% in another double blinded, placebo controlled study). Other antihistamines to be considered include clemastine fumarate (.34 - .68 mg/cat BID) or cyproheptadine (2 mg/cat BID; may cause polyphagia and behavioral effects). Each antihistamine is generally given a 2 - 3 week trial period to assess efficacy.

7. Pentoxifylline: This phosphodiesterase inhibitor has been noted to significantly benefit a small percentage of dogs with atopic dermatitis. While studies utilizing pentoxifylline in the treatment of feline atopy are currently lacking, anecdotal data would suggest that it may significantly benefit some atopic cats. The drug appears to be well tolerated in cats. Dosage that has been used is 10 mg/kg twice daily.

8. Testing and Hyposensitization: Hyposensitization has been reported to benefit anywhere from 60% to 78% of cases (Trimmer AM et al, Clin Tech Small Anim Pract, 2006). Testing to determine allergens for inclusion in hyposensitization protocols may either be with intradermal testing or in vitro serology or both. It is interesting to note that recent studies (Diesel A et al, 24th Proc. North American Dermatology Forum, 2009 - utilizing Heska technology and Bexley J et al, Proc. 6th WCVD in Vet Dermatology, 2008) showed no significant difference between the detection of allergen-specific IgE in atopic vs healthy cats. Data from either intradermal testing or in vitro serology appear to be associated with relatively similar success rates of hyposensitization (Trimmer AM et al, Clin Tech Small anim Pract 2006). Protocols for hyposensitization involve the gradual increase in volume and concentration of solution until the maintenance dosage (1/2 ml of 20,000 PNU/ml / week; aqueous allergens) is achieved. "Rush" immunotherapy ("induction phase" of hyposensitization all given in one day ; hyposensitization shot given every 30 minutes) has been conducted successfully in cats but, until there has been more experience with this protocol, it should be used with great caution (Trimmer AM et al, Vet Dermatology, 2005). Cats whose only manifestation of atopy is asthma have shown variable responses to hyposensitization (Prost C, Vet Dermatology, 2004) (Trimmer AM et al, 20th Proc. NA Vet Dermatology Forum, 2008). Sublingual immunotherapy has also been used with some success in cats, although no commercial product is marketed for this

species (only marketed for dogs). Canine products and protocols are used for cats. They do appear to tolerate this method of immunotherapy well. Antihistamines or low dose, every other day glucocorticoids (e.g. prednisolone) can be used to keep individuals comfortable while awaiting the onset of benefit of hyposensitization. While there is some theoretic data to suggest that cyclosporine may inhibit the mechanism of response to hyposensitization, consideration can be given to using cyclosporine to control clinical signs while awaiting the onset of benefit of hyposensitization. There is anecdotal data to suggest that this combination, in a clinical setting, does not appear to affect time to onset of hyposensitization.

9. Cyclosporine - Atopica for cats, Novartis; 100 mg/ml. The longest shelf life is 2 months after the bottle is opened.
 - a. Earlier work (usually using a dosage of 5 mg/kg/day) has shown modified cyclosporine to be beneficial in controlling the signs of atopy in 70% of patients. In studies done by Novartis (and submitted as part of their Original New Animal Drug Application), cats were treated with 7 mg/kg/day. 78% of 144 treated cats had an excellent to good response within 6 weeks of starting therapy.
 - b. In general, the initial benefit of cyclosporine is usually noted within 10 – 28 days of initiating therapy, although it may take 1-3 months of daily therapy to see the maximal benefit. Some clinical manifestations of atopy may not respond as well as others (e.g. indolent ulcers, eosinophilic granulomas being slower to respond / less responsive).
 - c. If only a partial response is noted, consider increasing the dosage by 20 – 25% (often will be more effective).
 - d. In the Novartis studies, cyclosporine was given with food or slightly after feeding. Although many owners (35%) continued to give the drug with food on a long term basis, many opted for just squirting it in the mouth (65%).
 - e. In the Novartis study, about 15% of patients required daily therapy to maintain response; about 20% could be managed with every other day therapy and 65% with twice weekly therapy.
 - f. In 205 treated cats (144 of the above noted cats and a number of other treated cats), side effects were common (vomiting/retching/regurgitation in 35 %, weight loss in 20%, diarrhea in 15%, decreased appetite in 14%, lethargy in 14%, hypersalivation in 11%, behavior change in 9%, ocular discharge in 7%, sneezing in 5.4% and gingivitis/hyperplasia in 4.4%). In the majority of cats, these signs were transient and

did not warrant discontinuation of the medication. The drug was discontinued in 6.8% for the following reasons: weight loss, anorexia, vomiting, diarrhea, hypersalivation, lethargy, hepatic lipidosis (2 cats), jaundice, upper respiratory signs, toxoplasmosis (one cat), anemia, bacterial dermatitis, seizure. Laboratory side effects were minor and included increases in glucose and cholesterol (but not out of the normal range). In cats that were treated with 3 times the recommended dose (i.e. 21 mg/kg/day), significant increases in cholesterol, glucose, BUN and Creatinine and APTT were noted (all just above the normal range).

- g. In our experience, the upper GI side effects of cyclosporine may be averted by stopping cyclosporine until the signs abate, then re-instituting therapy, and/or by freezing the capsule a few hours prior to administration or by administering an anti-emetic (metoclopramide or maropitant). For some cats who do not like the taste of the liquid or who hypersalivate excessively, consideration can be given to using the canine Atopica, which comes in a capsule form.
- h. Screening for “internal” manifestations of cyclosporine therapy is usually not carried out in young and middle aged cats. In older cats, or cats with significant health problems, we suggest that therapy be antedated by screening laboratory work, which is then repeated in one month and then again 3-4 months after starting therapy. Monitoring can be done every 6-12 months thereafter.
- i. Cats treated with 3 times the recommended dose of cyclosporine (21 mg/kg/day) and who had previously been vaccinated (FCV, FPV, FeLV, FHV-1 and rabies) had vaccine titers decrease but these titers did remain adequate both before and after booster vaccination. In contrast, cats on this high dose of cyclosporine failed to develop titers to a novel vaccine (FIV) while being treated with Atopica.
- j. In cats seropositive for toxoplasmosis, oocyst shedding is not reactivated by cyclosporine and cats infected with *T. gondii* prior to CsA administration failed to develop clinical signs after the administration of CsA. However, cats without titers (not previously exposed to toxoplasmosis) and with high cyclosporine concentrations may develop fatal infections after exposure. The routine performance of *Toxoplasma* titers prior to the initiation of cyclosporine in cats is controversial. In light of the fact that a positive titer does not predict for the re-activation of the disease and many cats may actually go on to develop toxo. titers while on cyclosporine, but do not develop disease, makes their value highly questionable. However, a negative titer in a cat treated with high blood cyclosporine values may make this individual very prone to

developing severe toxoplasmosis. Cats on cyclosporine should not be allowed to hunt and should be fed cooked or processed food.

- k. Monitoring of blood cyclosporine concentrations is also of questionable value. Blood concentrations do not appear to predict for clinical response (Novartis NADA). Because of the great variability in gastrointestinal absorption of cyclosporine in cats, we do recommend the performance of cyclosporine “trough” concentrations (cyclosporine measured just before the next daily dosing) in cats who are on longer term, daily therapy. Values greater than 1000 ng/ml appear to predict for immunosuppression which may significantly predispose to infection. Individuals on every other day or twice weekly therapies are very unlikely to have these higher values. For individuals who are not responding to therapy, consideration can be given to looking at trough levels to see if they are low (thereby warranting increasing the dose). Trough concentrations <50 – 100 are likely inadequate. There is some suggestion that samples evaluated at peak post pill values (2 hours) are more reflective of therapeutic immunosuppression. At this time, values should likely be no higher than 2000 ng/ml?

It should be noted that there are several methods available for measuring cyclosporine concentrations. HPLC detects only the parent compound. Other assays (e.g. TDx assay; one of the most commonly available commercial assays in the US) measure both the parent compound and its metabolites (most of which are not active). If using the TDx assay, a conversion factor (TDx value X 0.5 for the cat) must be used to calculate actual cyclosporine concentrations. The laboratory being used for the cyclosporine assay should be queried as to their recommendations for a conversion factor. Laboratories that currently run cyclosporine concentrations include North Carolina State and Auburn University.

10. Chlorambucil has also been of benefit (usually along with standard, anti-inflammatory/antipruritic dosages of steroids, as noted above) in treating refractory atopy. The recommended dose of chlorambucil is 0.1 - 0.2 mg/kg q 24 hrs until 75% improvement in clinical signs, then this dose given every other day. Adverse effects to be monitored for include bone marrow suppression and hepatotoxicity (i.e. should be normal liver enzymology prior to treatment; recheck liver enzymes at 2-3 weeks and 4-6 weeks in to therapy; CBC and platelet count every three weeks while on daily therapy, gradually taper off during every other day therapy).

11. Megestrol acetate may be considered a "last ditch" alternative for treating feline atopy, in light of potential side effects (polyphagia / weight gain, PU/PD, personality and behavioral changes, pyometra or stump pyometra, mammary hyperplasia, mammary neoplasia, diabetes mellitus and adrenal suppression). Remission of clinical signs can often be achieved with an oral dose of 2.5 - 5.0 mg/cat every 48 hours for 1-3 weeks. This is followed by weekly maintenance dosages.