In Practice

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Journal:	*In Practice*
Manuscript ID	INPRACT.2015.100401.R1
Article Type:	Clinical
Date Submitted by the Author:	n/a
Complete List of Authors:	Buckley, Laura ; University of Liverpool, School of Veterinary Science
Keywords:	Cats, Allergy, Skin, Pruritus, Dermatitis

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Introduction

Feline dermatology presents a number of challenges; individual diseases can be problematic to diagnose due to the more subtle and varied nature of skin lesions in cats compared to those commonly seen in dogs. In feline allergic skin disease, the diagnostic challenge is increased further because cats present with one or more of four patterns of disease rather than the more typical character and distribution of lesions seen with canine hypersensitivity dermatoses. Cats are also generally more solitary animals and secretive in their behaviour, which can lead to the absence of important clues in the clinical history. In terms of treatment of allergic skin disease there can be challenges both in the administration of treatment and in the comparatively poor treatment responses seen in some patients.

This article reviews the important steps in achieving a diagnosis of and successfully managing feline allergic skin disease, with particular reference to head and neck excoriations/pruritus which can be one of the more challenging presentations of feline allergic skin disease to manage.

Disease pathogenesis

Unlike canine disease, feline allergic skin disease (FASD) is poorly understood. The term feline atopic dermatitis is avoided by some dermatologists due to uncertainty about the significance of IgE in the development of skin lesions. What is known is that the histological pattern of cutaneous inflammation that develops in cats with hypersensitivity dermatitis is similar to that seen in humans and dogs. FASD is thought to develop, as in human and canine disease, in association with internal (genetic) predisposing factors and external stimuli. The proposed major external 'triggers' of disease flares include flea saliva, food and environmental allergens and result in clinical signs associated with flea bite hypersensitivity dermatitis (FBHD), food-induced hypersensitivity dermatitis (FIHD; cutaneous adverse food reaction) and non-flea, non-food-induced hypersensitivity dermatitis (NFNFIHD; feline atopic dermatitis), respectively. One study reported that 25% of cats with NFNFIHD had concurrent food allergy, flea allergy or both (Halliwell 1997). It is also likely that a form of FASD, similar to canine atopic-like dermatitis and human intrinsic atopic dermatitis, exists, in which an external allergenic trigger cannot be identified but clinical signs persist despite elimination of other differential diagnoses of pruritus. Contact dermatitis, another type of FASD, is not covered in this article, as it is uncommon compared to the other forms and presents with a more distinctive set of skin lesions that are associated with direct contact with an offending substance.

The diagnosis of feline allergic skin disease

In order to achieve long-term success in the management of FASD, it is essential that an accurate diagnosis be made. The diagnosis of FASD is a clinical one; it is made based on compatible history and physical examination findings and diagnostic tests are then performed to eliminate differential

diagnoses. The most of common of these being ectoparasite infestation and microbial infection. Finally, diagnostic trials muste be performed to identify the type of allergic skin disease or more specifically, the trigger for the hypersensitivity dermatitis. The major steps in achieving a definitive diagnosis of FASD are shown in Figure 1.

The diagnostic challenge in cats is in making the clinical diagnosis. A typical history includes a young age of onset (6 months – 32 years; approximately 75% cases), presence of pruritus, lack absence of contagion (except for some cases of FBHD) and response to appropriate doses of glucocorticoids. Unfortunately, for many cases of FASD, the most important of these historical clues are not present as cats may present later in life, and the owners have not observed self-trauma due to the secretive nature of cats and/or signs of flea infestation have not been observed as cats are highly efficient groomers. FBHD presents at any age and FIHD, although more common in young cats, can develop in mature cats (4-5 years old) and rarely in kittens and geriatric cats. Where owners have not observed self-trauma, the following signs provide evidence of pruritus: presence of linear excoriations (especially around the head and neck), broken hair shafts in areas of reduced coat density (this may need to be confirmed microscopically), increased incidence of hair balls and hairs embedded in the gingival sulci and/or dorsal tongue.

Unlike canine atopic dermatitis that usually presents with clear evidence of pruritus and lesions very typical in their character and distribution, cats with FASD present with one or more of four disease patterns. These include head and neck excoriations/pruritus (HNEP; Figures 2 and 3), symmetrical self-induced alopecia (Figures 4 and 5), miliary dermatitis and lesions of the eosinophilic granuloma complex (eosinophilic or indolent ulcer; Figure 6, eosinophilic plaque; Figure 7, eosinophilic granuloma; Figure 8). The major skin lesions associated with the patterns are summarised in Table 1.

Identification of one or more of the four patterns increases the suspicion of FASD but does not confirm it, nor does it inform the clinician as to the underlying trigger. In 2012, Favrot and others published two sets of diagnostic criteria to assist in making a clinical diagnosis of non-flea induced hypersensitivity dermatitis (i.e. FIHD or NFNFIHD); the first set is for cats presenting with pruritus and the second for pruritic cats following elimination of FBHD (Table 2). Clinically, FIHD and NFNFIHD are indistinguishable and despite the availability of the diagnostic criteria, differential diagnoses should still be carefully eliminated. The major differential diagnoses and diagnostic tests used to eliminate them are also summarised in Table 1. Uncommonly in FASD, sneezing, conjunctivitis, chronic coughing and/or feline asthma may be present in addition to skin lesions and gastrointestinal signs can be present more commonly in cats with FIHD.

In all cases of suspected FASD a strict flea control trial and elimination diet must be performed to rule out FBHD and FIHD respectively. This is particularly important in cats presenting with HNEP as a large multicentre study by Hobi and others (2011) reported that 38% and 64% of cats presented with neck and facial lesions in association with FBHD and FIHD

respectively. Suspected cases that have failed to respond to an initial trial should therefore, undergo a second trial.

The elimination diet should involve feeding a novel protein and carbohydrate for 6-8 weeks. If the full dietary history is unknown a hydrolysate diet may have to be used. It can be very challenging to perform an appropriate trial due to some cats being particular about what they eat and cats with outdoor access being fed by neighbours and/or the local wildlife. In these cases a selection of diets may need to be trialed and the cat may need to be gradually weaned onto the new diet. Cats that have access to food out of doors may need to be restricted to the house for the duration of the trial, although this can produce further problems if the stress induced by the change in environment exacerbates the allergic skin disease or leads to behavioural overgrooming. In addition, further undesirable outcomes including inappropriate urination, aggression and feline lower urinary tract disease may result from changes to the cat's environment.

The flea control trial should include use of an adulticide with rapid flea knockdown in both the affected cat and all in contact animals, plus treatment of the environment with a combined adulticide and insect growth regulator for 6-8 weeks. For cats with intermittent episodes of disease the length of both trials should be chosen to span a period over which clinical signs are expected to develop based on the history.

Management

The management of FASD is life long and can be broadly split into four treatment categories that aim to target the suspected pathogenesis. These include allergen avoidance and allergen specific immunotherapy (ASIT), anti-inflammatories and immunomodulators, avoidance of flare factors and skin barrier care. Treatment must be individualised and take into account patient factors including severity of disease, general health status, home environment (including risk of exposure to flea bites), predisposition to secondary microbial infections and tolerance of systemic and topical therapy. Client factors must also be considered and include financial constraints and ability to administer medications (including available time and physical constraints).

Cats presenting with severe inflammatory skin lesions (eosinophilic plaques and granulomas) and/or cats with severe pruritus and self trauma (HNEP) will require an initial focus on anti-inflammatory/immunomodulatory treatments to bring their skin lesions under control. For welfare reasons this treatment may need to be started before completion of diagnostic trials and achievement of a definitive diagnosis. In these cases, rapidly acting anti-inflammatories such as glucocorticoids are very useful as they can be used in sufficient doses (see below) and duration (usually 2-4 weeks) to control the clinical signs at the start of the diagnostic trials then tapered before the end of the trials to determine if clinical signs recur.

Once a definitive diagnosis is made and severe skin lesions have been brought under control, additional treatments can be added for long-term maintenance and systemic anti-inflammatory treatments can be tapered. In

cats with severe disease such as those presenting with HNEP and lesions of the eosinophilic granuloma complex, long term use of systemic anti-inflammatory/immunomodulatory treatment is often required. In these cases it is important to use enough treatment initially to bring the clinical signs under control then use additional treatments to try to reduce the dose and ~~dose~~ frequency of systemic drugs in the longer term. For example, topical glucocorticoids such as hydrocortisone aceponate can be used daily to treat flares of focal disease and on a twice weekly basis for known problem areas, alongside a tapered dose of the systemic treatment.

The clinical benefit of polypharmacy has to be balanced with animal tolerance and owner compliance, but one of the main advantages of its use is the potential to reduce the dose, and therefore the risk of adverse effects, of potent systemic treatments. When planning a long-term management protocol for allergic skin disease, treatments from each of the four categories should be considered.

Allergen avoidance and allergen specific immunotherapy (ASIT)

Cases experiencing flares in association with flea bites or food should be managed long term by avoiding the offending allergen. In cases of FBHD, aggressive adulticidal flea control should be maintained for the affected animal, in contacts and the environment for life. For cases of FIHD, the offending food(s) should be determined via re-challenge with individual ingredients and avoided long term. In cases where these diseases have been ruled out, environmental allergen IgE serology or intradermal testing can be performed and where positive results are obtained, ASIT can be considered to try to reduce the incidence of disease flares associated with exposure to environmental allergens. Avoidance of environmental allergens is challenging and rarely successful due to the ubiquitous nature of these proteins. ~~This treatment~~ ASIT is generally well tolerated and appears to be safe for the long term management of NFNFIHD. The reported response rate is 50-75% (Roosje and others 2002), however, it is ~~rarely~~ not always successful as a sole form of therapy (most likely due to the complex pathogenesis of NFNFIHD) and as it can take up to 12 months to see the full effects, all cases will need anti-inflammatory/immunomodulatory treatment in their initial management plan. ~~The reported response rate to ASIT is 50-75% (Roosje and others 2002) and it appears to be safe for long-term management of NFNFIHD.~~

Anti-inflammatories and immunomodulators

Glucocorticoids

FASD, like allergic skin disease in other species, usually responds well to treatment with systemic glucocorticoids. Some feline cases, however, require high dosages and some can be refractory to treatment. Oral treatment with prednisolone at starting doses of 1-2 mg/kg once daily are usually effective, although in some cases higher doses ~~of up to 4 mg/kg once daily~~ can be required. A recent study by Ganz and others (2013) demonstrated that methylprednisolone at a mean dosage of 1.4mg/kg once daily for 1-2 weeks was a very effective and safe treatment in achieving remission. Cats were

then maintained on 0.5 mg/kg every 48 hours. If the owner cannot administer tablets, injectable dexamethasone solution can be trialled. This is given by mouth or added to food at 0.1 mg/kg per day (induction dose) and 0.05 to 0.1 mg/kg every 3 days (maintenance dose).

Response to systemic glucocorticoids should be assessed every 7-14 days with the aim to maintain the cat on the lowest alternate day (or less frequent) dose that keeps disease in remission. If no response is seen, additional therapy should be considered in order to avoid excessive use of glucocorticoids. Where possible, depot corticosteroid preparations should be avoided due to the inability to withdraw treatment if adverse effects are encountered and, conversely, the inability to increase the dose if insufficient response is seen.

Care must be taken with the long-term use of potent glucocorticoids due to the risk of adverse effects. A study of 14 cats treated daily with prednisolone or dexamethasone suggested that dexamethasone induces greater diabetogenic effects than equipotent doses of prednisolone (Lowe and others 2009). Although cats seem to be more tolerant to systemic glucocorticoids than dogs, adverse effects including polydipsia, polyphagia, changes in weight, diabetes mellitus, urinary tract infection, iatrogenic hyperadrenocorticism, congestive heart failure, demodicosis and gastric ulceration can be seen.

Ciclosporin

Ciclosporin is a calcineurin inhibitor that exerts an immunomodulating effect via, amongst other actions, suppression of T lymphocyte function. It is licensed for use in cats in oral liquid form at 7 mg/kg once daily (Atopica Cat, Novartis Animal Health UK Ltd). A number of studies have demonstrated ciclosporin to be effective in the treatment of NFNFIHD and as effective as prednisolone (1mg/kg SID) at the licensed dose. As with dogs, once daily treatment should be continued for four weeks and if a good response is seen, treatment can be tapered to alternate day and then twice weekly therapy. Cats that relapse on alternate day therapy can be managed on daily treatment, reducing the dose to the lowest that maintains remission.

Ciclosporin, used at the licensed dose, is well tolerated by most cats, with main adverse effects limited to mild gastrointestinal disturbances (Heinrich and others 2011). Some reports have suggested a link between cases of toxoplasmosis and neoplasia. The cited cases of neoplasia, however, occurred following immunosuppression with a combination of ciclosporin and prednisolone prior to renal transplantation. Treatment with prednisolone and ciclosporin may also increase the risk of toxoplasmosis, however, the disease appears to be rare at the licensed dose of ciclosporin. *Toxoplasma*-naïve cats may be at a slightly higher risk of developing clinical toxoplasmosis during treatment and preventative measures include avoiding raw meat, keeping cats indoors, and fitting two bells to a collar to make hunting less successful. Healthy serologically positive cats, however, don't appear to be at risk of recrudescence of latent disease. Toxoplasma serology should therefore be

considered prior to commencement of treatment, along with FIV and FeLV testing as per data sheet recommendations.

Hydrocortisone aceponate

Hydrocortisone aceponate (HCA) is a non-halogenated, double ester glucocorticoid licensed for topical use in dogs as a 0.0584% spray (Cortavance, Virbac Ltd). Unlike conventional topical glucocorticoids, HCA is metabolised within the skin into a largely inactive form, allowing it to maintain local potency without the risk of systemic adverse effects (Brazzini and Pimpinelli 2002). A recent study (Schmidt and others 2012) evaluated the efficacy of daily or alternate day application of the commercially available 0.0584% HCA spray in ten cats with presumed allergic skin disease. There were significant improvements in both clinical lesion and pruritus scores over the 56-day study period. Ease of application of the spray, as scored by owners in the study, increased significantly with time and most owners rated the drug's efficacy as good or excellent. During the study, two sprays of HCA were applied to a 10 x 10 cm area of lesional skin daily for 28 days and reduced to alternate day therapy if there was a greater than 50% improvement in clinical lesion and pruritus scores. The response to treatment was rapid and most of the clinical improvement was seen within 14 days. Only one cat was withdrawn from the study due to poor treatment efficacy and no adverse effects were reported in any of the cats. The study suggests HCA is effective and safe for the treatment of FASD, although further controlled studies are required.

Oclacitinib

Oclacitinib is a novel drug that inhibits cytokines involved in allergic skin inflammation and pruritus via the inhibition of Janus kinase (JAK) enzymes. It is licensed for the treatment of canine atopic dermatitis at 0.4-0.6mg/kg twice daily for 14 days then once daily for maintenance therapy (Apoquel, Zoetis). A recent pilot study reported efficacy in a small number of cats with NFNFIHD, treated at the licensed dose for dogs over 28 days (Ortalda and others 2015). There was a reduction in skin lesions and pruritus scores in 6/12 and 5/12 cats respectively. No adverse effects were reported and owners judged ease of administration as good or excellent. This small study suggests that oclacitinib may be an option for the treatment of some cats with NFNFIHD, however, licensed treatments with a greater strength of evidence for efficacy should be prioritised. Due to the lack of long-term treatment data, and as per datasheet recommendations for long-term treatment in dogs, periodic monitoring of complete blood count and serum biochemistry should be performed.

Interferon omega

Anecdotal reports suggest that twice weekly or weekly subcutaneous injections of 2.5MU interferon omega (Virbagen, Virbac Ltd) can be effective and well tolerated in some cats with FASD. The mode of action is unknown, but is thought to be immunomodulatory. However, only a few cats have been treated and the long-term safety and efficacy is unknown. Interferon omega should therefore be reserved for cases that have failed to respond to licensed treatments with proven efficacy.

Progestagens

Megoestrol acetate (Ovarid, Virbac Ltd) is licensed for the management of lesions associated with FASD. Due to the risk of severe adverse effects including weight gain, diabetes mellitus, adrenocortical suppression, pyometra and mammary hyperplasia, and the availability of safer, more efficacious drugs, its use is not recommended.

Avoidance of flare factors

Flare factors are anything capable of exacerbating pruritus in animals with allergic skin disease. They include parasitic infestations, microbial infections, extremes of temperature/humidity and stress/anxiety (e.g. changes in the home environment). Although secondary microbial infections are known to be less common in FASD as compared to canine and human disease, both secondary ~~bacterial~~ staphylococcal pyoderma and *Malassezia* dermatitis have been reported. All FASD cases presenting with flares of pruritus should therefore undergo skin surface cytology to assess for microbial overgrowth/infection and treated appropriately. Microbial overgrowths and superficial bacterial infections should be managed using topical antimicrobial therapy. Although cats may be less tolerant of bathing, they may be more accepting of antimicrobial wipes (e.g. CLX Wipes, Vetruus) and sprays (e.g. Vetericyn Plus, Innovacyn Inc.) applied via cotton wool. For cats prone to recurrent microbial overgrowths, regular use of topical antimicrobial therapy on a twice-weekly basis should help to reduce the frequency of infection.

Skin barrier care

Little is known about the role of skin barrier dysfunction in the development of FASD but it is thought, as with canine and human disease, to form part of the pathogenesis and steps should therefore be taken to improve skin barrier care. As above, topical therapy with skin soothing shampoos, moisturisers and humectants may be limited in cats and care needs to be taken with leave-on therapies due to their meticulous grooming behaviour. Oral essential fatty acid supplementation can be trialled along with topical lipid complexes applied either with the use of a protective collar or to areas that the cat cannot groom.

Conclusion

There are a number of challenges with both the diagnosis and management of FASD. Identification of one or more of the patterns of FASD along with the use of Favrot's criteria assist with the diagnosis but differential diagnosis must be carefully eliminated. In all cases, a robust flea control trial and elimination diet must be performed. In cases that are more challenging to manage e.g. those presenting with HNEP, ~~further~~ repeat trials may be considered if no response is seen in the first instance in order to be certain that these triggers are eliminated. Additionally, all cases of suspected FASD failing to respond to appropriate treatment should have their diagnosis reviewed and repeat or further investigations e.g. treatment trial for *Demodex gatoi* infestation should be considered. The approach to management of FASD should focus on the four treatment categories that target the main areas of disease pathogenesis. It is of great importance to bring severe pruritus and skin lesions under control with adequate therapy before switching to safe, lifelong maintenance therapy.

MCQs

1) Which of the following is one of Favrot's criteria that can be used to assist in the diagnosis of FASD in cats presenting with pruritus prior to the exclusion of FBHD?
    a. Presence of crusting over the face and neck
    b. Absence of erosions/ulcerations on the front limbs
    c. Presence of ulceration affecting the footpads
    d. Absence of nodules/tumours
2) Which of the following body regions have been ~~are commonly~~ associated with both food-induced hypersensitivity dermatitis and flea bite hypersensitivity dermatitis?
    a. Ventral abdomen
    b. Face and neck
    c. Dorsal lumbosacral region
    d. Interdigital skin
3) What is the main indication for performing allergy testing in cats?
    a. To confirm a diagnosis of feline non-flea, non-food induced hypersensitivity dermatitis (NFNFIHD)
    b. To confirm a diagnosis of food-induced hypersensitivity dermatitis (FIHD)
    c. Following a diagnosis of NFNFIHD to identify environmental allergens for avoidance
    d. Following a diagnosis of NFNFIHD to identify environmental allergens for used in allergen specific immunotherapy
4) Which of the following ~~drugs~~ therapies ~~are~~ is licensed for use in cats for the management of FASD?
    a. C~~Prednisolone and c~~iclosporin
    b. ~~Ciclosporin and A~~allergen specific immunotherapy
    c. Hydrocortisone aceponate ~~and prednisolone~~
    d. ~~Ciclosporin and O~~oclacitinib
5) Which treatment group should be used initially in cats presenting with severe head and neck excoriations or pruritus?
    a. Allergen avoidance and allergen specific immunotherapy
    b. Anti-inflammatories and immunomodulators
    c. Avoidance of flare factors
    d. Skin barrier care

Answers

1) d
2) b
3) d
4) a
5) b

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