

## Establishment of diagnostic criteria for feline nonflea-induced hypersensitivity dermatitis

Claude Favrot\*, Jean Steffant†, Wolfgang Seewald†, Stefan Hobi\*, Monika Linek‡, Geneviève Marignac§, Thierry Olivry¶, Luc Beco\*\*, Claudia Netti††, Jacques Fontaine‡‡, Petra Roosjes§§, Kerstin Bergvall¶¶, Svetlana Belova\*\*\*, Stefanie Koebrich†††, Didier Pin‡‡‡, Marcel Kovalik§§§, Sabrina Meury\* and Sylvia Wilhelm\*

\*Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zürich, Zürich, Switzerland

†Novartis Animal Health, Basel, Switzerland

‡Tierärztliche Spezialisten, Hamburg, Germany

§Unité de Parasitologie, École Nationale Vétérinaire d'Alfort, Maisons-Alfort, France

¶Department of Clinical Sciences and Center for Comparative Medicine and Translational Research, Raleigh, NC, USA

\*\*Clinique Vétérinaire, Spa, Belgium

††Vetderm.ch – Dermatologie und Allergologie für Tiere,

Tieraerztliche Spezialiste, Hüneberg, Switzerland

‡‡Clinique Vétérinaire, Bruxelles, Belgium

§§Division of Clinical Dermatology, Department of Clinical Veterinary Medicine, Ve, Berne, Switzerland

¶¶Department of Clinical Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden

\*\*\*Department of Therapy, Institute of Veterinary Medicine and Animal Science, Esto, Tartu, Estonia

†††Kleintierpraxis, Neulussheim, Germany

‡‡‡Unité de Dermatologie, VetAgro Sup Campus Vétérinaire, Marcy L'Étoile, France

§§§Veterinary Dermatology Unit, Division of Veterinary Clinical Sciences, The Hospital for Small Animals, The Royal (Dick) School of Veterinary Studies, The University of Edinburgh, Edinburgh, UK

Correspondence: Claude Favrot, Clinic for Small Animal Internal Medicine, Dermatology Department, Vetsuisse Faculty, University of Zürich, Winterthurerstrasse 260, 8057 Zürich, Switzerland. E-mail: cfavrot@vetclinics.uzh.ch

### Sources of Funding

This study was funded by Novartis Animal Health, Basel, Switzerland.

### Conflict of Interest

Jean Steffant and Wolfgang Seewald are full-time employees of Novartis Animal Health.

### Abstract

**Hypersensitivity dermatitides (HD) are commonly seen in cats, and they are usually caused by environmental, food and/or flea allergens. Affected cats normally present with one of the following clinical reaction patterns: head and neck excoriations, usually symmetrical self-induced alopecia, eosinophilic skin lesions or miliary dermatitis. Importantly, none of these clinical presentations is considered to be pathognomonic for HD skin diseases, and the diagnosis of HD is usually based on the exclusion of other pruritic diseases and on a positive response to therapy. The objectives of this study were to propose sets**

**of criteria for the diagnosis of nonflea-induced HD (NFHD). We recruited 501 cats with pruritus and skin lesions and compared clinical parameters between cats with NFHD (encompassing those with nonflea, nonfood HD and those with food HD), flea HD and other pruritic conditions. Using simulated annealing techniques, we established two sets of proposed criteria for the following two different clinical situations: (i) the diagnosis of NFHD in a population of pruritic cats; and (ii) the diagnosis of NFHD after exclusion of cats with flea HD. These criteria sets were associated with good sensitivity and specificity and may be useful for homogeneity of enrolment in clinical trials and to evaluate the probability of diagnosis of NFHD in clinical practice. Finally, these criteria were not useful to differentiate cats with NFHD from those with food HD.**

Accepted 20 June 2011

### Introduction

Cats with hypersensitivity dermatitides (HD) are usually presented to veterinarians with one of the following clinical reaction patterns: head and neck excoriations, symmetrical self-induced alopecia, miliary and/or eosinophilic dermatitis.<sup>1–5</sup> Flares of these HD are normally triggered by one or more of several groups of allergens that include airborne environmental, dietary ingested and flea salivary injected allergens. Unfortunately, the clinical presentations mentioned above are neither pathognomonic for HD, nor are they specific for any particular group of allergens. The final diagnosis of HD is based principally on the exclusion of other pruritic diseases. Additionally, responses to dietary restriction–provocation challenges, to flea control or to immune-modulating therapy (e.g. allergen-specific immunotherapy, glucocorticoids or ciclosporin) are necessary to establish the aetiological diagnosis of food-associated HD, flea-bite HD and nonflea, nonfood HD, respectively.<sup>1,2,5,6</sup>

The large phenotypic variability of feline nonflea HD (NFHD) has prevented attempts to establish diagnostic criteria for this syndrome. Employing an epidemiological approach and adapted mathematical methods, we recently validated two sets of criteria for the diagnosis of another heterogeneous HD, canine atopic dermatitis.<sup>7</sup> These sets of criteria are associated with sensitivity and specificity up to 80% and are expected to enhance the homogeneity of recruitment in clinical studies.

The study reported here used a similar approach to that used for the diagnosis of canine atopic dermatitis to establish criteria for diagnosing NFHD in cats.

## Materials and methods

### Study population

Twenty veterinary dermatologists working in eight different European countries (Belgium, Estonia, France, Germany, Greece, Sweden, Switzerland and UK) and the USA participated in this study. The clinicians selected cats with pruritus provided that sufficient information was available, that a single definitive diagnosis had been made and that the diagnosis could be unequivocally included in one of the three groups of interest [i.e. NFHD, flea HD and OD (other diseases); see next subsection]. Most cats selected for this study were those described in a previous publication.<sup>8</sup>

For every cat enrolled in this study, a set of relevant historical (signalment, way of life and previous treatments) and clinical parameters (skin lesions and nondermatological signs) were recorded as described previously (Table 1).<sup>8</sup> Most cases (350) were selected prospectively, but cats could also be included retrospectively (151) if most parameters could be retrieved from medical records, if the diagnosis was final and if diagnostic procedures were fully documented and consistent with the procedures used for prospective cases.

### Subject grouping by diagnosis

Cats included in the study had to exhibit pruritus that was either chronic (longer than 2 months duration) or recurrent (more than two

episodes). A standardized diagnostic procedure was used, which included skin scrapes and control of ectoparasites, skin cytology to rule out bacterial and yeast infections when the skin was inflamed and a fungal culture to rule out dermatophytosis. In addition, other tests (skin biopsies or PCR) could be performed when deemed necessary for confirming a specific diagnosis.

In the first group of cats, the diagnosis of NFHD was based on history, the presence of one of the four typical patterns (head and neck excoriations, symmetrical self-induced alopecia, miliary and/or eosinophilic dermatitis) and the exclusion of other pruritic conditions, such as flea HD.

To confirm or exclude the diagnosis of food-induced HD (food HD) in these cats with NFHD, a 6–8 week restriction diet followed by a 2 week (maximum) challenge with the previous diet (a dietary restriction–provocation test) had to be carried out. Investigators were free to select the most appropriate type of diet for this procedure, and the diagnosis of food HD was confirmed after remission of signs during the restriction phase and subsequent flare after challenge with the original diet. Cats with NFHD whose signs did not respond to dietary restriction were given the more precise diagnosis of nonflea, nonfood HD, provided that they had responded adequately to treatment with allergen-specific immunotherapy, glucocorticoids, ciclosporin or type I histamine receptor antagonists. If a restriction diet had not been done, was done improperly or was of doubtful interpretation, the cat was considered as having an unspecified HD (UHD), and such cats were excluded from further analysis. In summary, the group of cats with NFHD encompassed those with food HD and those with nonflea, nonfood HD.

In a second group of cats, the diagnosis of flea-bite-associated HD (flea HD) was made because of suggestive signs and a satisfactory response to flea control as chosen by the investigators.

A third group of cats encompassed those with other pruritic diseases (OD). This group included all those that did not have NFHD or flea HD.

In order to standardize the data, diagnoses made by the investigators were verified by one of the authors (C.F.) by assessing the consistency of the recorded parameters with the final diagnosis (e.g. a cat with a final diagnosis of food HD should have had signs that responded adequately to an elimination diet and relapsed upon challenge; a cat with a final diagnosis of notoedric mange should have had pruritus that responded completely to antiparasitic therapy). If a discrepancy between signs and diagnosis, or diagnosis and outcome, was discovered, the case was excluded from further analysis. Finally, cases with more than one diagnosis (e.g. food HD + flea HD) were not included in the analysis to avoid confounding factors leading to the improper allocation of diagnostic criteria.

### Diagnostic criteria

For statistical analyses the following parameters were included: the presence and the type of lesion; the dominant clinical lesional pattern; the presence of otitis; the severity of pruritus; and the age at onset. Some parameters were subjectively but logically grouped together to establish new criteria; for example, the parameters 'at least two body sites affected' and 'at least two lesions among eosinophilic lesions, symmetrical alopecia, miliary dermatitis and erosion/ulceration of the face' were assembled. Each parameter was then recorded as 'present', 'absent' or 'unknown' where the information was not available.

### Group comparisons (univariate analysis)

*Data analysis was undertaken in three consecutive steps.* Firstly, the group of cats with NFHD was considered as a homogeneous group, and it was compared with the population of cats with other pruritic conditions (i.e. flea HD + OD). The frequency of occurrence of all recorded parameters was compared between both populations (NFHD versus flea HD + OD). For each individual parameter its sensitivity, specificity and possible correlation with the diagnosis of NFHD were determined. Correlations between parameters and diagnoses

**Table 1.** History and clinical features of pruritic cats

|                       |                                    |
|-----------------------|------------------------------------|
| Number                |                                    |
| Owner                 | Spell                              |
| Cat                   | Spell                              |
| Breed                 | Spell                              |
| Sex                   | Male/Female                        |
| Age                   | Spell                              |
| Age at onset          | Spell                              |
| Pruritus 1–10         | 1–10                               |
| Pruritus at onset     | Y/N                                |
| Dominant pattern      | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| First lesion at onset | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Localization          |                                    |
| Head/face             | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Ears                  | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Chin                  | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Lips                  | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Oral/mouth            | EP/EU/EG/NA                        |
| Neck                  | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Rump/tail             | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Forelimbs             | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Hindlimbs             | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Front paws            | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Hindpaws              | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Thorax                | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Sternum/axilla        | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Flanks                | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Abdomen               | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Perineum              | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Dorsum                | M/EP/EU/EG/IU/SA/NSA/ER/P/FC/SE/NA |
| Otitis externa        | Y/N                                |

Abbreviations: EG, eosinophilic granuloma; EP, eosinophilic plaque; ER, erythema; EU, erosions/ulcerations; FC, fat chin; IU, indolent ulcers; M, miliary dermatitis; N, no; NA, not applicable, no lesions; NSA, nonsymmetrical alopecia; P, pustules; SA, symmetrical alopecia; SE, seborrhoea; and Y, yes.

were considered significant at the level of  $P < 0.001$  to account for the possibility of multiple comparisons. Parameters with significant correlations, a sensitivity of at least 75% and a specificity of at least 10% (or the reverse) were selected as potentially useful for the diagnosis of NFHD.

In a second step, cats with food HD were compared with those with nonflea, nonfood HD. Comparisons were made as described in the preceding paragraph.

Finally, cats with flea HD were excluded from the analysis to mimic the classical work up of pruritic cats, which often begins with an evaluation of the response to flea control. Consequently, cats with NFHD were then compared solely with those with OD. Comparisons between the two groups were made as described above.

## Generation of criteria sets (multivariate analysis)

In order to generate sets of criteria to optimize the diagnosis of NFHD, a simulated annealing technique was used. Simulated annealing is a heuristic (i.e. 'trial-and-error') method for maximization of a function over a multidimensional space; in this case, sensitivity multiplied by specificity over the entire range of diagnostic criteria. This method works by repeated addition and deletion of parameters.<sup>9</sup> For each step, different settings of criteria were used to include either as many criteria as possible or as many cats as possible. In the first setting cats with no information for one of these criteria were excluded from analysis, while in the other setting criteria that were not documented in all included cats were excluded from the analysis. As a result not all cats enrolled in the study were taken into consideration for all analyses.

Series of sets including 5–10 criteria were selected through the mathematical procedure described above. These sets corresponded to the highest sensitivity, specificity and combination of both (i.e. selectivity defined as sensitivity  $\times$  specificity). The various sets of criteria were evaluated carefully based on the number of criteria in a set, their sensitivity, specificity and selectivity, as well as their possible use in routine practice. To establish a set of criteria that could be used in general practice, sets containing criteria difficult to record or rarely recorded were not retained.

## Statistical software

Descriptive statistics and simulated annealing were performed using SAS 9.1.3 (SAS Institute, Cary, NC, USA). Comparisons between populations of cats were carried out using chi-squared and Fisher's exact tests using Instat 3 (Graphpad, San Diego, CA, USA). Proportions were considered statistically significant if  $P$  was  $<0.05$  after multiplication of the computed  $P$ -value by the number of tested parameters.

## Results

### Study population and diagnoses

Five hundred and one cats were initially included in this study. There were 238 cats with NFHD (including 61 cats with food HD, 98 with nonflea, nonfood HD and 79 with UHD), 137 with flea HD and 126 with OD. Five cats with an inaccurate and/or more than one diagnosis and all 79 cats with UHD were later excluded from the study according to the study protocol. Data from 417 cats were finally analysed. As mentioned above, most of these cats have already been described in a previous study,<sup>8</sup> but some of these cats were later removed because they had developed another disease in the meantime ( $n = 11$ ), while some new cases were also included ( $n = 10$ ).

### Comparisons between groups

#### *Comparison 1: cats with NFHD versus those with pruritus of other cause (flea HD + OD)*

Eight criteria were significantly correlated with the diagnosis NFHD ( $P < 0.001$ ), and they had a sensitivity of at least 75% and a specificity of at least 10% (or the reverse) for this diagnosis (Table 2). Most criteria exhibited a high sensitivity but low specificity. The highest sensitivity was seen with criteria more prevalent in cats with flea HD or OD, especially the absence of other animals in the household and the absence of nonsymmetrical alopecia, as well as the absence of lesions on the rump and/or tail or dorsum. Other highly sensitive criteria positively correlated with the diagnosis of NFHD were as follows: (i) the presence of lesions in two or more than two body areas; and (ii) the presence of one of the following reaction patterns: eosinophilic dermatitis, symmetrical alopecia or head and neck erosions/ulcerations.

The highest specificity was observed when erosions or ulcerations were seen on the neck or chin. None of the criteria was both highly sensitive ( $>75\%$ ) and highly specific.

A total number of 402 cats were taken into account for assessing the combination of criteria for the diagnosis of NFHD in multivariate analysis. When all criteria were used simultaneously, a set emerged as having the best selec-

**Table 2.** Criteria for the diagnosis of nonflea-induced hypersensitivity dermatides (NFHD)

| Criterion                                            | OD + flea HD |      | NFHD |      | Correlation | P-value   | Sens. | Spec. | Pos. PV | Neg. PV |
|------------------------------------------------------|--------------|------|------|------|-------------|-----------|-------|-------|---------|---------|
|                                                      | Neg.         | Pos. | Neg. | Pos. |             |           |       |       |         |         |
| No other animals in the household                    | 57           | 192  | 14   | 139  | 0.18        | 0.0001    | 0.91  | 0.24  | 0.42    | 0.80    |
| NSA is not the dominant pattern                      | 51           | 198  | 13   | 140  | 0.16        | 0.0005    | 0.92  | 0.21  | 0.41    | 0.80    |
| EP or EG or IU or SA, or head/face/lips/ears/neck EU | 74           | 175  | 14   | 139  | 0.24        | $<0.0001$ | 0.91  | 0.30  | 0.44    | 0.84    |
| Lesion of EU on chin or neck                         | 200          | 49   | 95   | 58   | 0.20        | $<0.0001$ | 0.38  | 0.80  | 0.54    | 0.68    |
| No M or NSA on rump or tail                          | 45           | 204  | 8    | 145  | 0.18        | $<0.0001$ | 0.95  | 0.18  | 0.42    | 0.85    |
| No lesion on rump or tail                            | 81           | 168  | 19   | 134  | 0.23        | $<0.0001$ | 0.88  | 0.33  | 0.44    | 0.81    |
| No lesion on rump or tail or dorsum                  | 109          | 140  | 37   | 116  | 0.20        | $<0.0001$ | 0.76  | 0.44  | 0.45    | 0.75    |
| At least two sites affected                          | 71           | 178  | 16   | 137  | 0.21        | $<0.0001$ | 0.90  | 0.29  | 0.44    | 0.82    |

Abbreviations: EG, eosinophilic granuloma; EP, eosinophilic plaques; EU, erosions/ulcerations; IU, indolent ulcer; M, miliary dermatitis; Neg., criteria not met (i.e. negative of a negative criterion means that there is presence of the parameter); NSA, nonsymmetric alopecia; Pos., criteria met; SA, symmetric alopecia.

Positive predictive value (Pos. PV), negative predictive value (Neg. PV), sensitivity (Sens.) and specificity (Spec.) correspond to the diagnosis NFHD.

**Table 3.** Criteria set for the diagnosis of feline NFHD

|                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------|
| Presence of at least two body sites affected                                                                            |
| Presence of at least two of the four following clinical patterns:                                                       |
| Symmetrical alopecia                                                                                                    |
| Miliary dermatitis                                                                                                      |
| Eosinophilic dermatitis                                                                                                 |
| Head and neck erosions/ulcerations                                                                                      |
| Presence of symmetrical alopecia                                                                                        |
| Presence of any lesion on the lips                                                                                      |
| Presence of erosions or ulcerations on the chin or neck                                                                 |
| Absence of lesions on the rump                                                                                          |
| Absence of nonsymmetrical alopecia on the rump or tail                                                                  |
| Absence of nodules or tumours                                                                                           |
| Fulfilment of five of the eight criteria gives a sensitivity of 75% and a specificity of 76% for the diagnosis of NFHD. |

tivity (Table 3). Both sensitivity and specificity were about 75% when five of these eight criteria were fulfilled.

*Comparison 2: cats with NFHD versus those with pruritus of other origin but not with flea HD*

In a second step, cats with NFHD were compared with cats with OD after the exclusion of those diagnosed with flea HD (Table 4). Most of the criteria significantly correlated with the diagnosis of NFHD were highly specific, especially the typical lesion patterns, which included eosinophilic dermatitis, symmetrical alopecia and head and neck erosions/ulcerations. Likewise, the presence of any lesions on the abdomen and the presence of pruritus at onset of the disease were found to be good markers of feline NFHD because they are associated with relatively high selectivity. In contrast, the presence of nodules or tumours was, as expected, strongly associated with the diagnosis of OD.

Two hundred and sixteen cats were taken into account for determining a set of criteria for the diagnosis of NFHD after exclusion of flea HD. When all criteria were used simultaneously in the multivariate analysis, the best set of criteria was associated with a sensitivity and specificity

**Table 5.** Criteria set for the diagnosis of feline NFHD after exclusion of flea HD

|                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------|
| Presence of pruritus at onset                                                                                             |
| Presence of at least two of the following classical clinical reaction patterns:                                           |
| Symmetrical alopecia                                                                                                      |
| Miliary dermatitis                                                                                                        |
| Eosinophilic dermatitis                                                                                                   |
| Head and neck erosions/ulcerations                                                                                        |
| Presence of at least two sites affected                                                                                   |
| Presence of miliary dermatitis as a dominant pattern                                                                      |
| Presence of eosinophilic dermatitis or symmetrical alopecia or erosions/ulcerations on the head, face, lips, ears or neck |
| Presence of nonsymmetrical alopecia on the rump, tail or hindlimbs                                                        |
| Presence of symmetrical alopecia on the abdomen                                                                           |
| Absence of erosions/ulcerations on the forelimbs                                                                          |
| Absence of lesions on the sternum or axilla                                                                               |
| Absence of nodules or tumours                                                                                             |
| Fulfilment of six of these 10 criteria gives a sensitivity of 90% and a specificity of 83% for the diagnosis of NFHD.     |

of 90 and 83%, respectively, when six of the 10 criteria were fulfilled (Table 5).

*Comparison 3: cats with food HD versus those with non-flea, nonfood HD*

The univariate analyses are not presented in detail because the only significant correlation uncovered was the presence of seborrhoea, which was highly specific for nonflea, nonfood HD. For the multivariate analysis 153 cats were taken into account. Sets of criteria with acceptable sensitivity, specificity and selectivity were not discovered.

## Discussion

To the best of our knowledge, this study is the first attempt to use a mathematical approach to validate sets of criteria for the diagnosis of feline NFHD.

**Table 4.** Cats with NFHD compared with other cats

| Criterion                                                                 | OD (without flea HD) |      | NFHD |      | Correlation | P-value | Sens. | Spec. | Pos. PV | Neg. PV |
|---------------------------------------------------------------------------|----------------------|------|------|------|-------------|---------|-------|-------|---------|---------|
|                                                                           | Neg.                 | Pos. | Neg. | Pos. |             |         |       |       |         |         |
| Absence of nodules or tumours                                             | 19                   | 68   | 8    | 121  | 0.23        | 0.0015  | 0.94  | 0.22  | 0.64    | 0.70    |
| Eosinophilic dermatitis or head and neck pruritus or symmetrical alopecia | 28                   | 59   | 10   | 119  | 0.32        | <0.0001 | 0.92  | 0.32  | 0.63    | 0.74    |
| At least two sites affected                                               | 34                   | 53   | 10   | 119  | 0.38        | <0.0001 | 0.92  | 0.39  | 0.69    | 0.77    |
| Pruritus at onset                                                         | 45                   | 42   | 14   | 115  | 0.45        | <0.0001 | 0.89  | 0.52  | 0.73    | 0.76    |
| Eosinophilic dermatitis                                                   | 85                   | 2    | 112  | 17   | 0.19        | 0.0014  | 0.13  | 0.98  | 0.89    | 0.42    |
| Eosinophilic plaques                                                      | 84                   | 3    | 108  | 21   | 0.20        | 0.0008  | 0.16  | 0.97  | 0.88    | 0.44    |
| Symmetrical alopecia on the abdomen                                       | 83                   | 4    | 85   | 44   | 0.35        | <0.0001 | 0.34  | 0.95  | 0.92    | 0.49    |
| Symmetrical alopecia as dominant pattern                                  | 76                   | 11   | 83   | 46   | 0.26        | <0.0001 | 0.36  | 0.87  | 0.81    | 0.48    |
| At least two reaction patterns                                            | 80                   | 7    | 83   | 46   | 0.32        | <0.0001 | 0.36  | 0.92  | 0.87    | 0.49    |
| Dominant pattern eosinophilic plaques or symmetrical alopecia             | 75                   | 12   | 74   | 55   | 0.31        | <0.0001 | 0.43  | 0.86  | 0.82    | 0.50    |
| Abdomen, any lesion                                                       | 68                   | 19   | 61   | 68   | 0.31        | <0.0001 | 0.53  | 0.78  | 0.78    | 0.53    |
| Symmetrical alopecia on the abdomen                                       | 70                   | 17   | 61   | 68   | 0.33        | <0.0001 | 0.53  | 0.80  | 0.80    | 0.53    |

Abbreviations: Neg., criteria not met (i.e. negative of a negative criterion means that there is presence of the parameter); Pos., criteria met; Sens., sensitivity; and Spec., specificity.

In this analysis, cats with flea HD were excluded. Positive and negative predictive values correspond to the diagnosis NFHD.

A limitation of this study is that some of the diagnoses (e.g. flea or food HD) can be difficult to rule out with certainty, especially when only one restriction diet or therapeutic trial is carried out. As a result, the authors cannot guarantee that all cats were allocated in an appropriate study group. However, the large number of differing factors between groups, especially between cats with NFHD and flea HD, support the hypothesis that most cats were included in a relevant group.

When each individual criterion was analysed separately, it was not possible to identify any one that had both high sensitivity and specificity for the diagnosis of NFHD. While some criteria exhibited a high sensitivity and a poor specificity, some had the reverse. This lack of criteria with good selectivity (sensitivity  $\times$  specificity) is not unexpected considering the phenotypic variability known for this presentation and the long list of differential diagnoses.

It might be tempting to combine individual criteria with both high sensitivity and specificity to establishing sets of criteria for the diagnosis of NFHD. However, such an approach could be misleading because the criteria themselves could be correlated together. The correlation between any selected criterion and the diagnosis might be, in fact, quite different in cats satisfying or not satisfying this parameter. Also several criteria could be redundant if correlated together. For example, a criterion A could be correlated with a criterion B that has both high sensitivity and specificity. If criterion B were met, criterion A could be found also to be highly correlated with NFHD. But if criterion B were not met, criterion A would no longer be relevant for characterizing the disease. This phenomenon implies analysing the effect of a combination of criteria simultaneously rather than independently. As a result, a more sophisticated optimization method (i.e. simulated annealing) was used because it calculates actual changes in sensitivity and specificity when single criteria are added to or deleted from the diagnostic sets.

Despite an apparent variability in cats with NFHD, the multivariate analysis discovered several sets of criteria with sufficient sensitivity and specificity to be useful for diagnosis. As expected, when cats with flea HD were removed from the study group both sensitivity and specificity of the criteria were greatly improved. This observation is consistent with the experience of most veterinary dermatologists, who would consider that flea HD is the main differential diagnosis of NFHD and as a result should be ruled out first before making a diagnosis of NFHD.

Interestingly, the sets of criteria selected by simulated annealing were related to the nature and distribution of skin lesions, but they did not include any parameters relevant to the demographics, the environment, associated diseases or prior therapies, although all this information had been recorded and was available for inclusion. It is possible that our population of cats was not large enough to identify an association between NFHD and these non-lesional parameters. Alternatively, this observation might indicate a lack of obvious relationship between NFHD, the environment or other diseases.

Some criteria were found to be common to the two sets proposed by the simulated annealing. The presence

of skin lesions on more than one body region appears to increase the likelihood of NFHD. The simultaneous presence of more than one of the typical presentations, such as head and neck erosions/ulcerations, symmetrical self-induced alopecia, eosinophilic dermatitis and miliary dermatitis, does dramatically enhance the probability of NFHD. The presence of symmetrical alopecia or head and neck erosions/ulcerations alone was also found in the two sets of criteria, which also suggests a strong association with NFHD.

In contrast to the usual perception of its association with flea HD, miliary dermatitis appeared to be a valid criterion for the diagnosis of NFHD, especially when lesions were not dorsally distributed.

Criteria derived from the univariate analysis provided interesting information, especially when examining criteria obtained by comparison of cats with NFHD with the total population of cats or after exclusion of those with flea HD. After exclusion of cats with flea HD, some of the criteria with high specificity were no longer found to be significantly different between groups. Criteria such as an absence of lesions on the dorsum, rump or tail were not specific for NFHD when cats with flea HD were removed from the analysis. This observation suggests that these dorsal lesions do characterize mostly cats suffering from flea HD, a fact known for a long time.<sup>1</sup>

Likewise, when cats with flea HD were excluded the presence of several animals in the household was no longer a highly specific criterion for the diagnosis NFHD. This could probably be explained by a higher frequency of multipet households in the population of cats with flea HD. Indeed, a higher exposure to fleas in households with several animals or a higher frequency of cats living outdoors when cats are housed with other animals is to be expected.

After exclusion of cats with flea HD, we uncovered additional criteria with high specificity that had not been identified previously when comparing cats with NFHD with those having OD. Lesions of symmetrical alopecia, lesions localized on the abdomen or a dominant pattern of eosinophilic lesions appeared to be highly specific for the diagnosis feline NFHD. While lesions present on the dorsum seem to be mostly indicative of flea HD, those localized on the abdomen, head or neck seem to characterize NFHD.

Interestingly, we were not able to uncover a set of criteria that separated cats with nonflea, nonfood HD from those with food HD. This situation mirrors that seen in dogs with atopic dermatitis. As mentioned elsewhere, head and neck erosions/ulcerations, which are generally considered typical of food HD, do appear to occur more often in cats with food HD, but are far from being pathognomonic for this hypersensitivity.<sup>1,2</sup>

Depending on the setting, the sensitivity and specificity of the newly determined sets of criteria vary from 71 to 82%. It should consequently be emphasized that using these criteria alone would lead to wrong diagnoses in a substantial number of cases. A proper work up of pruritic cats is consequently mandatory and should include at least the exclusion of ectoparasites, fungal and bacterial diseases, as well as some neoplastic and viral conditions. The role of food as a cause of nonseasonal pruritus

should always be taken into account and properly assessed.

We propose to use these criteria, especially those reported in Table 5, because of their high specificity and sensitivity, in the framework of clinical trials to ensure the homogeneity of study groups. Veterinary practitioners could also use the criteria of Table 3 before any work up to evaluate the probability of diagnosis of NFHD. After having performed the above-mentioned work up, criteria from Table 5 would seem to be more appropriate to confirm the diagnosis of NFHD after exclusion of flea HD.

## References

1. Foster AP. Diagnosing and treating feline atopy. *Veterinary Medicine* 2002; 97: 226–40.
2. Foster AP, Roosje PJ. Update on feline immunoglobulin E (IgE) and diagnostic recommendations for atopy. In: August JR, ed. *Consultations in Feline Internal Medicine*, 4th edn. Philadelphia, PA: W.B. Saunders, 2004: 229–38.
3. Prélard P, Guaguère E, Freiche V *et al.* The allergic cat. *Pratique Médicale et Chirurgicale de l'Animal de Compagnie* 1999; 34: 437–47.
4. Prost C. Les dermatoses allergiques du chat. *Pratique Médicale et Chirurgicale de l'Animal de Compagnie* 1993; 28: 151–64.
5. Scott DW, Miller WH, Griffin CE. Chapter 8. Skin immune system and allergic skin diseases. In: Muller and Kirk's *Small Animal Dermatology*, 6th edn. Philadelphia, PA: W.B. Saunders Co., 2001: 543–666.
6. Prost C. Diagnosis of feline allergic diseases: a study of 90 cats. In: Von Tscharner C, Kwochka KW, Willemse T, eds. *Advances in Veterinary Dermatology*, vol. 3. Oxford: Blackwell Sciences, 1998: 516–7.
7. Favrot C, Steffan J, Seewald W *et al.* A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. *Veterinary Dermatology* 2010; 21: 23–31.
8. Hobi S, Linek M, Marignac G *et al.* Clinical characteristics and causes of pruritus in cats: a multicentre study on feline hypersensitivity-associated dermatoses. *Veterinary Dermatology* doi: 10.1111/j.1365-3164.2011.00962.x.
9. Kirkpatrick S, Gelatt CD Jr, Vecchi MP. Optimization by simulated annealing. *Science* 1983; 220: 671–80.

**Résumé** Les dermatoses par hypersensibilité (HD) sont fréquemment rencontrées chez le chat et sont habituellement liées à des allergènes environnementaux, alimentaires et/ou de puce. Les chats atteints présentent habituellement un des patrons réactionnels cliniques suivants : excoriations de la tête et du cou, alopecie auto-infligée symétrique, lésions éosinophiliques cutanées ou dermatite miliare. Cependant, aucune de ces présentations cliniques ne sont considérées comme pathognomoniques pour les dermatoses par hypersensibilité. Leur diagnostic repose habituellement sur l'exclusion des autres dermatoses prurigineuses et à une bonne réponse au traitement. Les objectifs de cette étude étaient de proposer des sets de critères pour le diagnostic des HD non-liées aux puces (NFHD). Cinq cent un chats prurigineux et lésionnels ont été inclus dans l'étude. Les paramètres cliniques ont été comparé entre les chats avec NFHD (englobant ceux avec une HD non-liée aux puces, non-liée à l'alimentation et ceux liés à l'alimentation), avec une HD liée aux puces et les autres dermatoses prurigineuses. A l'aide de technique de simulations, nous avons établi deux sets de critères pour deux situations cliniques différentes : 1) le diagnostic de NFHD dans une population de chats prurigineux et 2) le diagnostic de NFHD après exclusion des chats avec HD liée aux puces. Ces sets de critères ont été associés avec une bonne sensibilité et une bonne spécificité et peuvent être utiles pour le diagnostic de NFHD en pratique clinique. Enfin, ces critères n'ont pas été utiles pour différencier les chats atteints de NFHD de ceux avec une HD liée à l'alimentation.

**Resumen** Los dermatitis por hipersensibilidad (HD) se observan con frecuencia en gatos, y son causados generalmente por los alérgenos ambientales, en el alimento y/o de las pulgas. Los gatos afectados se observan normalmente con una de las siguientes presentaciones clínicas: excoriaciones de la cabeza y cuello, alopecia generalmente simétrica autoinducida por el mismo gato, lesiones de piel eosinofílicas o dermatitis miliar. Pero es de resaltar que ninguna de las presentaciones se considera patognomónica de HD, y el diagnóstico definitivo de HD se basa generalmente en la exclusión de otras enfermedades pruríticas de la piel y en una respuesta positiva a la terapia. Los objetivos de este estudio fueron proponer los criterios para el diagnóstico de HD no inducida por pulgas (NFHD). Reclutamos 501 gatos con prurito y lesiones de piel y comparamos parámetros clínicos entre los gatos con NFHD (abarcando animales con hipersensibilidad no causada por pulgas ni por alimentos y las causadas por alimentos HD), la HD inducida por pulgas y otras condiciones pruríticas. Usando técnicas de simulación de alineamiento, establecimos dos grupos de criterios propuestos para dos diversas situaciones clínicas: 1) el diagnóstico de NFHD en una población de gatos pruríticos y 2) el diagnóstico de NFHD después de la exclusión de gatos con HD inducidos por pulgas. Estos criterios fueron asociados a buenas sensibilidad y especificidad y pueden ser útiles para la homogeneidad de la inscripción en ensayos clínicos así como para evaluar la probabilidad de un diagnóstico de NFHD en práctica clínica. Finalmente, estos criterios no fueron útiles para distinguir gatos con NFHD de hipersensibilidad causada por componentes alimentarios.

**Zusammenfassung** Überempfindlichkeitsdermatitiden (HD) werden häufig bei Katzen gesehen, wobei sie meistens durch die Umwelt-, Futter- und/oder Flohallergene verursacht werden. Betroffene Katzen werden normalerweise mit einem der folgenden klinischen Reaktionsmuster präsentiert: Kopf-und-Hals Exkoriationen, üblicherweise symmetrische selbst-induzierte Alopezie, eosinophile Hautveränderungen oder miliare Dermatitis. Es ist bedeutend, dass keine dieser klinischen Präsentationen als pathognomonisch für HD Hauterkrankungen erachtet wird und es sich bei der Diagnose von HD normalerweise um eine Ausschlussdiagnose handelt, wobei alle anderen juckenden Hauterkrankungen ausgeschlossen werden und eine positive Reaktion auf eine Therapie stattgefunden hat. Die Ziele dieser Studie waren eine

Zusammenstellung von Kriterien für die Diagnose einer nicht durch Flöhe induzierten HD (NFHD) zu präsentieren. Wir rekrutierten 501 Katzen mit Juckreiz und Hautveränderungen und verglichen die klinischen Parameter zwischen den Katzen mit NFHD (die solche mit nicht durch Flöhe verursachte, nicht durch Futter verursachte HD und solche mit HD durch Futter verursacht, umfassten), Floh-HD und anderen juckenden Erkrankungen. Mittels simulierter Abkühlungstechnik etablierten wir zwei Sets an vorgeschlagenen Kriterien für zwei unterschiedliche klinische Situationen: 1) die Diagnose von NFHD in einer Population von juckenden Katzen und 2) die Diagnose von NFHD nach Ausschluss der Katzen mit HD durch Flöhe. Diese Zusammenstellung an Kriterien waren mit einer guten Sensibilität und Spezifität gekoppelt und könnten sinnvoll sein, um eine Homogenität der Patienten bei klinischen Versuchen zu erreichen und um die Möglichkeit der Diagnose von NFHD in der klinischen Praxis zu bewerten. Abschließend muss man sagen, dass diese Kriterien für die Unterscheidung von Katzen mit NFHD und solchen mit HD durch Futtermittel nicht sinnvoll waren.

**要約** 過敏性皮膚炎 (HD) は猫で一般的に認められる、それらは通常、環境、食事および／あるいはノミアレルゲンによって起きる。罹患したネコは以下のうち1つ以上の臨床反応パターンを示す；頭部と頸部の表皮剥離、通常左右対称性の自己誘発性脱毛、好酸性皮膚病変、または粟粒性皮膚炎。重要なことは、それらの臨床症状はどれも1つもHD皮膚疾患の特徴的症状と考えられておらず、HDの診断は通常、その他のそう痒性疾患の除外と治療への反応に基づき行われる。この研究の目的は非ノミ誘発性HD(NFHD)のための診断基準を提案することである。著者らは501頭のそう痒および皮膚病変を示す猫で、NFHD(非ノミ、非食事と食事HDを含む)、ノミHD、その他のそう痒性疾患の間で臨床的なパラメーターの比較を行った。シミュレーションアニーリング法を用いて、我々は2つの異なる臨床的な状態に対する、2種類の基準の提案を確立した：1)そう痒を示すネコの集団内でのNFHDの診断、と2)ノミHDのネコを除外したあとのNFHDの診断。これらの基準の感度と特異性は良好であり、臨床試験での組み入れる症例の均一性と臨床でのNFHDの診断確度を評価するのに役に立つ可能性がある。最後に、これらの基準はNDHDと食事性HDの猫を鑑別するには有効でなかった。