Treatment of naturally occurring asthma with inhaled fluticasone or oral prednisolone: A randomized pilot trial

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Abstract

The objective of this study was to compare inhaled glucocorticoids with oral glucocorticoids for treatment of naturally occurring feline asthma. Secondary goals were to evaluate serum allergy testing results in cats and to quantify the effect of an inhaled glucocorticoid (fluticasone) on glucose homeostasis. Nine cats with asthma were enrolled on the basis of clinical signs, thoracic radiographic findings, and airway eosinophilia. Cats were randomized and 4 cats were treated with oral glucocorticoids and 5 cats with inhaled glucocorticoids, with a 7-day course of oral glucocorticoids overlapping at the start of therapy. Cats were evaluated at baseline and at 8 wk with thoracic radiographs, bronchoalveolar lavage, lung function testing, and fructosamine levels. Serum allergen panels were evaluated. All cats were clinically normal after treatment and had significantly improved airway eosinophilia and decreased nucleated cell count. No improvement was seen in radiographic changes after treatment with either therapy. Oral, but not inhaled glucocorticoids, caused a decrease in airway resistance, although cats in the inhaled group had a higher baseline resistance than those in the oral group. Fructosamine levels did not change with treatment. Fifty percent of cats tested positive for immunoglobulin E (IgE) antibodies. Asthma is a heterogeneous condition; individual cats responded well to both oral and inhaled glucocorticoids. Ongoing evaluation of the potential underlying causes and therapeutic options is warranted with a larger group of cats.

Résumé

L'objectif de l'étude était de comparer le traitement de l'asthme félin avec des glucocorticoïdes inhalés et administrés par voie entérale. Les objectifs secondaires étaient d'évaluer les résultats de tests d'allergies de chats atteints d'asthme félin et de quantifier l'effet d'un glucocorticoïde inhalé (fluticasone) sur l'homéostasie du glucose. Neuf chats atteints d'asthme félin ont été recrutés selon les signes cliniques, les trouvailles radiographiques et les évaluations cytologiques des voies aériennes (éosinophilie). Les chats ont été randomisés. Quatre chats ont été traités avec des glucocorticoïdes par voie entérale et cinq chats avec des glucocorticoïdes inhalés dont les 7 premiers jours ont été associés à l'administration de glucocorticoïdes par voie orale. Les chats ont initialement été évalués au moment du recrutement et puis à huit semaines avec des radiographies thoraciques, lavage bronchoalvéolaire, tests de fonction pulmonaire et dosage de la fructosamine. Des tests sériques d'allergènes ont également été évalués. Tous les chats ont eu une résolution des signes cliniques après le traitement et avaient une amélioration significative du compte éosinophilique du LBA. Aucune amélioration des lésions radiographiques suivant le traitement soit inhalé ou entéral n'a été observée. Seuls les glucocorticoïdes entéraux ont causés une diminution de la résistance des voies respiratoires. Toutefois les chats du groupe de traitement de glucocorticoïdes inhalés avaient, avant l'initiation du traitement, une résistance pulmonaire plus importante. Les niveaux de fructosamine n'ont pas changé significativement, et ce dans les deux groupes de traitement. 50 % des chats ont testé positif pour des anticorps IgE contre des allergènes inhalés communs. L'asthme est une entité clinique hétérogène; les chats ont individuellement bien répondu autant au traitement inhalé qu'au traitement entéral. L'étude des potentielles causes sous-jacente et des différentes options thérapeutiques sont recommandées dans une population plus grande de chats.

(Traduit par les auteurs)

Introduction

Feline asthma is estimated to affect up to 5% of cats (1). Feline asthma is similar to human asthma in many ways, including bronchial thickening, airway hyperreactivity and remodeling, excess mucus production, cough, and occasional respiratory distress (1–2). While the underlying cause of feline asthma is unknown, the disease may be mimicked by sensitization to Bermuda grass allergen (BGA) or *Ascaris suum*, which supports an allergic etiology (3). Asthma is diagnosed in a cat with a cough, wheeze, and/or respiratory distress by excluding other potential causes of these clinical signs, such as heartworm or lung worm infestation, heart failure, infection, or neoplasia (4). Diagnostic evaluation for affected cats includes thoracic radiographs, which typically document a bronchial pattern,

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and bronchoalveolar lavage (BAL) cytology, which demonstrates airway inflammation and eosinophilia (4). Treatment is directed at ameliorating airway inflammation through glucocorticoids (GCs) and rescue bronchodilators, as well as avoidance of potential triggers (5–7).

Glucocorticoids (GCs) are often administered orally in the form of prednisolone, although they can also be administered by inhalation or as a repositol, e.g., methylprednisolone acetate, or transdermal preparations. Repositol and transdermal medications are more commonly reserved for cats that may be harder to medicate. The efficacy of transdermal glucocorticoids has not been established.

Potential side effects of systemic oral glucocorticoids (O-GCs) include alterations in the hypothalamic-pituitary-adrenal (HPA) axis and derangements in glucose homeostasis, resulting in diabetes mellitus (DM), weight gain, and heart failure. It is thought that these adverse effects are minimized with the use of inhaled glucocorticoids (I-GCs) rather than O-GCs. Inhaled-GCs are most commonly used in humans as it has been demonstrated that delivering the therapeutic agent directly to the lungs is superior for long-term control of airway inflammation in humans with asthma (8).

Administering I-GCs to small children and domestic cats, however, requires the use of a spacer, as they are unable to follow instructions to use an inhaler directly. Due to the intrinsic differences between the nasal anatomy of a cat and a human, there are some disadvantages to the use of spacers with cats. Spacers may limit the dose reaching the lungs, as a certain percentage is swallowed rather than inhaled and some is also lost to the environment (9). This potentially limits the direct benefit of I-GCs and may negate any perceived GC-sparing benefit. Getting a cat to cooperate for aerosol administration and the prohibitive cost of inhaled GCs in the United States are other limitations to their use.

The best approach to therapy with glucocorticoids (GCs) for feline asthma is not known. The 2 common treatment approaches are oral prednisolone tapered to a dose low enough to control apparent clinical signs of cough, while minimizing side effects, or daily administration of inhaled GCs. It has been shown that resolution of clinical signs in humans is not universally associated with resolving airway inflammation and airway hyperreactivity (10). Similarly, evaluating the response to therapy for asthma in cats is challenging as the apparent resolution of clinical signs is not always associated with resolution of airway inflammation (11).

Unchecked airway inflammation may lead to progressive airway remodeling, excessive mucus production, and airway smooth muscle hypertrophy, with subsequent air-trapping and expiratory flow limitation. In humans, evaluation of lung function, specifically the forced expiratory volume in 1 s (FEV1), is widely used to better characterize expiratory flow limitation and response to therapy. While voluntary maximal expiratory effort is not possible in cats, similar information about flow limitation may be evaluated with flow-volume loops (12,13) and measurement of lung resistance (2,14). Radiographic improvement in response to treatment has been documented in cats with experimental asthma, but has not yet been evaluated in naturally occurring asthma (6).

Experimentally, Reinero et al (3) have recreated an asthma phenotype by sensitizing cats to Bermuda grass, while Kirshvink's group created similar airway changes following exposure to *A. suum* (6). Inhaled glucocorticoids (I-GCs) have a beneficial effect on decreasing airway eosinophilia mediated by exposure to Bermuda grass (7). Both O-GCs and I-GCs have been shown to decrease airway hyperresponsiveness and inflammation in cats sensitized to *A. suum* (6). No comprehensive evaluation has been done of the effects of treatment with I-GCs or O-GCs on the major aspects of naturally occurring asthma in cats, namely airway inflammation, anatomical/radiographical abnormalities, and lung function.

Glucocorticoid therapy, in any form, has the potential to alter the HPA axis, as well as to predispose a cat to the development of diabetes mellitus (DM). While it has previously been demonstrated that inhaled fluticasone suppresses HPA axis activity, the effect of fluticasone on glucose homeostasis, as assessed by fructosamine concentrations, has not been evaluated (6,7). Elevated fructosamine is considered to be an early marker for DM, and while elevations in fructosamine have been identified in healthy cats administered oral prednisolone (15,16), the effect of fluticasone on fructosamine is unknown. Finally, the specific inciting factor for allergic asthma is not often identified clinically. One pilot study (17) showed a marked increase in positive results for intradermal skin and serum testing in cats with asthma, which shows that specific inhalant allergies play a functional role in the development of the asthmatic phenotype.

The objective of this study was to compare the relative ability of inhaled fluticasone with oral prednisolone to resolve airway eosinophila and radiographic/clinical signs and to decrease airway resistance in naturally occuring feline asthma. The secondary goals were to report the effects of inhaled glucocorticoids (I-GCs) on glucose homeostasis and the results of serum allergy testing in cats with asthma.

Materials and methods

Study cats

Cats with naturally occurring asthma that had not previously been treated were prospectively recruited from the emergency and internal medicine services at the Foster Hospital for Small Animals at the Cummings School of Veterinary Medicine, Tufts University. Asthma was identified based on consistent signalment (>1 and <10 y old), clinical signs (cough, wheeze, and/or respiratory distress), a generalized bronchial or bronchointerstitial pattern on thoracic radiographs, and airway eosinophilia ($\geq 17\%$) on blind bronchoalveolar lavage (BAL) (18). Cats were excluded from participation if there was evidence of other underlying disease, such as heartworm or lungworm infestation, heart failure, other cardiopulmonary disease, or lack of sufficient airway eosinophilia. The study was approved by the clinical science review committee and the owners provided written informed consent before cats were enrolled in the study.

Study design

Cats were assigned to 1 of 2 groups using a randomization chart: i) O-GC group with administration of 5 mg of prednisolone by mouth twice daily for 14 d and then 5 mg of prednisolone once daily for 6 wk; or ii) I-GC group with administration of 5 mg of prednisolone once daily for the first 7 d and 110 μg of I-GC as fluticasone (Flovent HFA; GlaxoSmithKline, Research Triangle Park,

North Carolina, USA) administered twice daily for the duration of the study using a specially designed spacer and facemask (Aerokat Feline Aerosol Chamber; Trudell Medical, London, Ontario). Owners of cats randomized to the I-GC group were trained on use of the device. Prednisolone was provided to both groups as a compounded chewable tablet (Wedgewood Compounding Pharmacy, Swedesboro, New Jersey, USA). Cats were evaluated at baseline and then again after 8 wk of therapy. Each evaluation included thoracic radiographs, lung function testing, blind BAL, and serum fructosamine.

Thoracic radiographs. Computed radiographic (CR) images of the thorax from both time points were exported as DICOM images, anonymized to remove patient ID, name, and signalment, and then randomized by a single author (MVK) using an open source anonymizer (DICOM Cleaner; PixelMed Publishing, Bangor, Pennsylvania, USA). All studies were subsequently evaluated by a single observer (TJO), who was Board-certified by the American College of Veterinary Radiology and unaware of the radiograph acquisition time point. Images were viewed using a free and open source DICOM viewer (OsiriX Lite; PixmeoSARL, Geneva, Switzerland). The observer was able to manipulate the images by adjusting window level/width, zoom, and pan. The availability of left lateral, right lateral, dorsoventral, and ventrodorsal projections was documented.

Radiographs were given a score of 0 to 9 based on the severity of bronchial, interstitial, and alveolar patterns, with each pattern separately graded on a scale of 0 to 3, similar to methods described in previous studies (19,20). Bronchial patterns were graded as: (0) absent; (1) mild, with visualization of first generation bronchi; (2) moderate, with visualization of second generation bronchi; and (3) severe, with visualization of third generation bronchi. Unstructured interstitial patterns were graded as: (0) absent; (1) mild, with generalized slight increase in soft tissue opacity of lung parenchyma that did not blur the vascular margins; (2) moderate, with generalized or focal increased soft tissue opacity of the lung parenchyma that blurred some vascular margins; or (3) severe, with generalized increased soft tissue opacity of lung parenchyma that blurred all vascular margins in the affected lung lobe.

Structured interstitial patterns with any size of soft tissue opaque pulmonary nodules were not present in any cases and were therefore not graded. Alveolar patterns were graded as: (0) absent; (1) mild, with focal "fluffy" mild increase in soft tissue opacity of pulmonary parenchyma without visualization of vascular margins; (2) moderate, as presence of air bronchograms (unilateral or bilateral); or (3) severe, as presence of lobar signs (unilateral or bilateral). All grading was done in a single viewing session. Scores before and after therapy, for individual cats and for groups as a whole, were compared during statistical evaluation.

Lung function testing. Cats were briefly anesthetized with intravenous propofol [4 to 6 mg/kg body weight (BW), IV] and were intubated with standard size and length of endotracheal tube. After a standardized volume history (2 breaths to 25 cmH_2O), cats were ventilated at 8 mL/kg BW tidal volume with a peak inspiratory flow of 4.5 L/min, respiratory rate of 15 breaths/min, a fraction of inspired oxygen concentration of 30%, and 3 cmH_2O of positive end-expiratory pressure. Lung resistance (Rstat) was then calculated using the internal algorithm in a critical care ventilator (Puritan Bennett 840 Ventilator; Covidien, Boulder, Colorado, USA).

Bronchoalveolar lavage (BAL). After lung function was determined, blind BAL was carried out using 2 mL/kg BW of warmed saline, repeated 3 times, for a total of 6 mL/kg BW of lavage. All cats received 1 puff of albuterol (90 μg) after lung function was determined and before BAL. The lavage fluid was placed into tubes containing ethylenediamine tetraacetic acid (EDTA). Direct smears and cytocentrifuged preparations of the fluid were made. All slides were stained with a 2-part aqueous Romanowsky stain (Protocol Hemaspray; Fisher Health Care, Hampton, New Hampshire, USA) and an automated slide stainer (Aerospray Hematology Stat Slide Stainer 7122; EliTech Group, Puteaux, France) before being reviewed by 1 of 2 clinical pathologists, both Board-certified by the American College of Veterinary Pathology (JK, PB). Clinical pathologists were unaware of the cat's treatment status. The total nucleated cell count and the percentage of eosinophils were recorded.

Systemic effects. Serum fructosamine was evaluated at baseline and at the completion of the study.

Serum allergy testing. A single serum sample was collected at baseline and submitted to a reference laboratory (Allercept Serum Allergen; Heska, Loveland, Colorado, USA) to be tested for evidence of increased reactivity to common inhalant allergies. These included weeds (yellow dock, English plantain, lamb's quarters, rough pigweed, Russian thistle, short ragweed, burweed marsh elder, rough marsh elder, kochia, tall ragweed, mugwort, and common cocklebur); trees (bayberry wax myrtle, white ash, shagbark hickory, box elder, Eastern cottonwood, American elm, black birch, sugar maple, red mulberry, white oak, American sycamore, black walnut, yellow pine, quaking aspen, and red cedar); grasses (timothy grass, orchard grass, Johnson grass, sweet vernal, meadow fescue, smooth brome, perennial rye grass, red top grass, June bluegrass, and Bermuda grass); fungi *(Fusarium roseum, Penicillium notatum/chyrogenum, Aspergillus fumigatus, Cladosporium sphaerospermum,* and *Alternaria tenuis);* and environment *(Dermatophagoides pterinyssinus, Tyrophagus putrescentiae,* flea saliva, cat epithelium, *Dermatophagoides farinae,* and cockroach*)*.

Statistical analysis

Descriptive and summary statistics were calculated. Pre- and post-treatment values for individual patients as well as differences between groups were compared using a Wilcoxon rank-sum test or Fisher's exact test with a P-value < 0.05 considered significant.

Results

A total of 14 cats were enrolled and 9 cats successfully completed the 8-week study. Two cats were excluded after enrollment due to lack of sufficient airway eosinophilia (2% and 5%, respectively). One owner moved despite agreeing to participate in the study and the cat was lost to follow-up and 2 owners failed to administer medications as prescribed, despite verbal and written instructions. Of the 9 cats that completed the study, 8 were domestic short hairs and 1 was a domestic long hair. Four were spayed females and 5 were neutered males. The median age of cats was 2 y (range: 18 mo to 9 y) and the mean weight was 5 ± 1.1 kg. All cats were heartworm antigen and antibody negative, with no evidence of parasites on Baermann fecal sedimentation and fecal flotation. No cats had evidence of external parasites such as fleas.

Table I. Baseline characteristics of enrolled cats and response to therapy.

	BAL eosinophil % and total nucleated cell count/μL		Static resistance (Rstat; $cmH_2O/L/s$)		
Cat number	Baseline	Post-treatment	Baseline	Post-treatment	IgE-specific allergen
Inhaled glucocorticoid group					
1	58; 4880	43; 7520	57.7	56.6	*F. roseum*
2	48; 9450	19; 3800	36.6	32.67	*F. roseum*, flea saliva, *T. putrescentiae*
3	84; 21300	7; 1760	42	35	Negative
4	51; 7880	44; 834	39.3	33.4	Negative
5	42; 7420	1; 3370	42.33	81	Ragweed, cedar, flea saliva, *T. putrescentiae*, *D. farinae*
Oral glucocorticoid group					
6	64; 4960	20; 810	98.0	42.3	Not available
7	42; 3360	0; 2810	48.3	34.7	Negative
8	42; 2800	9; 3410	109.7	35.3	*T. putrescentiae*, *D. farinae*
9	54; 4650	2; 2240	81.3	32.3	Negative

BALF — bronchoalveolar lavage; immunoglobulin E-specific allergen is classified as either positive or negative; *F. roseum — Fusarium roseum; T. putrescentiae — Tyrophagus putrescentiae (dust mite); D. farina — Dermatophagoides farinae.*

Four cats were randomized to receive oral glucocorticoid (O-GC) therapy alone and 5 cats to receive inhaled glucocorticoids (I-GCs). All cats responded well to therapy and both owners and attending clinicians considered them clinically normal after 8 wk of treatment. No cats had labored breathing at any point in the study and owners reported that coughing had not been observed in the cats. Both forms of therapy were well-tolerated by cats and owners, and no owners reported difficulty giving the medications. Further information about clinical signs at home was not recorded.

Thoracic radiographs

Radiographs were available for review in 8 cats both before and after treatment. In 1 cat in the O-GC group, only post-treatment radiographs were available for review. In this cat (number 6), the post-treatment score was 4. In the 8 cats with pre- and post-treatment radiographs, the median score decreased insignificantly from 4 to 2 ($P = 0.11$). In the O-GC group ($n = 3$), the median pre-treatment score was 4 and the median post-treatment score was 3. Two cats had a decrease in score and 1 cat had an increase in score from pre- to post-treatment. In the I-GC group ($n = 5$), the median pre-treatment score was 4 (range: 1 to 5) and the post-treatment score was 2 (range: 1 to 3). Four of the 5 cats had a decrease in score and 1 cat increased from 1 to 3. There was no difference in the number of cats that improved radiographically or the degree of change between groups.

Airway eosinophilia

In accordance with the study design, all cats had airway eosinophilia at the time of enrollment. Airway eosinophilia decreased significantly in all cats ($P = 0.003$) from a median of 51% eosinophils to a median of 9%. There was a decrease of 48% to 6% in the O-GC group and a decrease of 51% to 19% in the I-GC group (Table I). There was no difference in reduction between groups as there was significant interindividual variation in response. Using 17% eosinophils as the therapeutic target point [based on normal eosinophil percentages proposed in previous articles (21,22)], 3 out of 4 cats (75%) in the O-GC group, compared to 2 out of 5 cats in the I-GC group, achieved this level of improvement ($P = 0.52$). Total nucleated cell count decreased significantly from a median of 4960/μL (range: 2880 to 21 300/μL) to 2810/μL (range: 810 to 5720/μL) with a $P = 0.03$.

Lung function testing. Results of lung function tests in individual cats are shown in Table I. The median lung resistance (Rstat) was 48.3 $cmH_2O/L/s$ (range: 36.6 to 109.7 $cmH_2O/L/s$). The baseline median Rstat was higher in the O-GC group at 89.7 $cmH_2O/L/s$ than in the I-GC group at 42 $cmH_2O/L/s$ ($P = 0.032$).

After treatment, the median Rstat for all cats decreased from 48.3 $cmH_2O/L/s$ to 35 $cmH_2O/L/s$ ($P = 0.02$). Within groups, the median Rstat in the O-GC group was lower after treatment at 35 $cmH_2O/L/s$ compared to 89.7 $cmH_2O/L/s$ at baseline (0.03), while in the I-GC group, the median Rstat after treatment was 35 $cmH_2O/L/s$, which was not statistically different from baseline (42 $cmH_2O/L/s$; $P = 0.54$).

There was no correlation ($r = 0.27$) between percentage of eosinophils in bronchoalveolar lavage fluid (BALF) and airway resistance. Cats with 50% or more eosinophils had a median Rstat of 57 $cmH_2O/L/s$ and cats with $< 17\%$ eosinophils had a median Rstat of 35 $cmH_2O/L/s$, although this was not significantly different ($P = 0.08$).

Fructosamine

There was no change in median fructosamine with treatment; median level before treatment was 217 μmol/L *versus* 227 μmol/L after treatment ($P = 0.86$). No cat developed hyperglycemia or any signs of polyuria/polydipsia/polyphagia.

Serum allergy testing

Serum allergy results were available for 8 cats. Four cats had no detectable allergen-specific IgE and 4 cats had evidence of detectable serum-specific IgE (Table I).

Discussion

In this small 8-week pilot clinical trial, treatments with both inhaled and oral glucocorticoids (I-GCs and O-GCs) were effective in eliminating clinical signs and reducing airway eosinophilia in cats with naturally occurring asthma. Both O-GCs and I-GCs were well-tolerated by all treated cats. Oral glucocorticoids (O-GCs) were associated with a more robust improvement in airway resistance than inhaled GCs in cats as measured using a critical care ventilator, although the baseline resistance was significantly higher in cats that were randomized to the O-GC group.

Interestingly, while all cats were clinically normal after therapy, there was persistent evidence of airway inflammation (eosinophilia) in 4 cats and evidence of increased airway resistance (> 50 $cmH_2O/L/s$) in 2 cats. This suggests that assessing response to therapy may require re-sampling of the airways, rather than just evaluating clinical signs and radiographs in order to truly resolve all changes associated with feline asthma.

In a similar study in horses comparing inhaled glucocorticoids and oral dexamethasone to treat equine asthma, both delivery methods improved airway function, with variable results on airway cytology (23). It has been demonstrated that fluticasone is more effective in long-term prevention and treatment of equine asthma than in acute improvement in a crisis (24) and the same may be true in cats. In human medicine, inhaled corticosteroids are the recommended first choice for treating asthma, although oral corticosteroids are acceptable if inhaled options are not available or in severe/refractory cases (8).

The underlying reason for development of spontaneous feline asthma is unknown. Since exposure to inhaled allergens, e.g., Bermuda grasses, has been effective in creating a model of feline asthma, immunotherapy has been proposed as a method of treating cats with spontaneous feline asthma. Interestingly, only half of the cats in this study showed evidence of serum IgE-specific reactivity. This is similar to a previous study (17) in which 34% of allergens tested were positive in cats with asthma. The cats that demonstrate serum IgE-specific reactivity may represent a cohort of cats that would respond to desensitization therapy, which was not evaluated in this study. Intradermal skin testing, which may be more specific for a true allergic phenotype, was not done in these cohorts and this may have led to a misrepresentation of cats with identified allergies.

This study evaluated airway eosinophilia as an outcome. The day-to-day repeatability of blinded BAL in cats is unknown, whereas it is considered to be reproducible in humans (25). This study used 17% eosinophils as a cutoff based on previous work (3) and used in prior studies (18,22). A more recent paper used 5% eosinophils as a cutoff for healthy cats (26). Using 5% as a cutoff, only 1 of 5 cats reached that target with I-GC and 2/4 cats with O-GC ($P = 0.52$). A more stringent cutoff for airway eosinophilia might therefore be considered in future studies. Airway eosinophilia has been identified as being related to enhanced pause (PENH), which is an indirect measure of airway resistance, in cats with chronic bronchitis that are challenged with carbachol (6). Similar results were not found in this small study, although cats with higher airway eosinophilia did have a nonsignificant increase in airway resistance.

This study used a critical care ventilator to characterize changes in airway resistance in cats with naturally occurring asthma. Airway resistance primarily reflects narrowing of the larger airways, with higher resistance associated with more airway narrowing. Similar to humans and horses, cats develop naturally occurring bronchoconstriction, which should lead to higher airway resistances. While testing of pulmonary function has been used extensively in human medicine and in research settings to characterize airway disease, there has been limited crossover to clinical veterinary patients, including cats (14).

In the Bernhard study, experimentally induced asthmatic cats had a baseline airway resistance as measured by ventilator mechanics of 55.2 ± 7.8 $cmH_2O/L/s$ (14). This was similar to the median of 48.3 $cmH_2O/L/s$ observed in the present study. Using dedicated equipment for testing pulmonary function, Dye et al (2) identified airway resistance of 38 to 45 $cmH_2O/L/s$ in mild to moderately affected cats with naturally occurring asthma. This supports the use of critical care ventilator mechanics as a reasonable surrogate for more dedicated equipment for testing pulmonary function. As more veterinary practices acquire critical care ventilators, the opportunity to routinely test lung function in practice is increasingly common and may be easily combined with collection of BALF (27). One significant limitation of this study was using baseline lung function testing, rather than following aerosol challenge with histamine or carbachol, as airway hyperresponsiveness is a key feature of asthma (6,28). We chose not to conduct bronchoprovocation in client-owned animals due to its associated risks.

There was no significant effect of treatment on the severity of radiographic scores for cats enrolled in either treatment arm of this study, which is similar to previous results in experimental models (6). The visible radiographic changes, i.e., bronchial pattern, associated with feline lower airway disease are the result of thickened bronchi/conducting airways. This thickening likely represents a summation of effects from smooth muscle hypertrophy, eosinophilic infiltrate, and mucus production resulting from chronic inflammation. While treatment will decrease mucus production and cellular infiltrates, it is not likely to fully reverse the airway remodeling, i.e., muscle hypertrophy, that occurs with this condition. Furthermore, given the lack of correlation between measured airway resistance and radiographic score, thoracic radiographs are probably not the most effective surrogate for assessing treatment efficacy, despite their wide availability.

In addition to potential limitations due to underlying non-reversible airway changes, other limitations of thoracic radiograph evaluation in this study included the use of a single observer, as well as differences in radiographic projections available for review, i.e., orthogonal *versus* single lateral, and radiographic technique, i.e., patient motion, rotation, or pulmonary underinflation.

The dose of I-GC administered in this study was chosen based on previous studies that used cats with induced airway disease (5–7). Based on the limited absorption due to conformation, some clinicians feel that a higher dose, e.g., 220 μg/puff, would be more effective. The ideal dose of inhaled glucocorticoids for cats remains to be determined. In a similar study using an asthma model, a higher dose of fluticasone (500 μg twice daily) combined with 50 μg of salmeterol was effective in decreasing airway eosinophilia and hyperresponsiveness (6).

Similarly, the dose of prednisolone chosen for the O-GC group was 5 mg every 12 to 24 h and it is possible that a higher dose

would be more effective. This study chose not to compound based on individual cat weights in order to more closely mimic a typical clinical approach.

One limitation of this study was the substantial variability in results of BAL, radiographs, and lung function testing for cats with clinical signs consistent with feline asthma. This natural variability may influence the severity of disease, as well as the response to therapy, and may reflect the difference in outcome in individual cats in this pilot study rather than a specific difference in treatment efficacy.

Another limitation included lack of *Mycoplasma* culture or polymerase chain reaction (PCR) in all cats. It is recognized that *Mycoplasma* infection or co-infection may be documented in cats with airway disease (29), although the role of *Mycoplasma* in feline respiratory disease is not known. *Bordetella bronchiseptica* has also been isolated in cats with cough (2,30). Additionally, despite randomization of the groups, the O-GC group had a significantly higher baseline resistance, suggesting that the underlying severity of disease might have been different from the I-GC group. Finally, it is possible that owners of cats in either group were less effective at administering the medication than they reported.

The most significant limitation of this pilot study was sample size; only 9 cats were ultimately enrolled and completed the study, with an additional 5 cats being enrolled, but not completing the study. A *post-hoc* analysis of blind BAL eosinophilia showed that 60 cats (30 per group) would have been required to demonstrate a significant difference between groups.

In conclusion, both oral and inhaled glucocorticoids (O-GCs and I-GCs) improve lung function and reduce airway eosinophilia. This pilot study was underpowered to detect a difference in therapeutic efficacy. Persistent airway inflammation after treatment was common, despite the apparent lack of clinical signs. Repeated BAL and/or pulmonary function testing may be necessary to document treatment efficacy for asthma as thoracic radiograph changes did not resolve with therapy. Further investigation is required to better elucidate the underlying causes of feline asthma, as well as to determine the most appropriate treatment options.

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Errata

The corresponding author has requested that the following changes be made to his article which appeared in the October 2020 issue (CJVR 2020;84:272–282).

Abstract

The objective of this study was to compare the efficacy of commercially available porcine circovirus type 2 (PCV2) and *Mycoplasma hyopneumoniae* vaccines. A total of 80 pigs was randomly divided into 6 treatment groups; 4 of the groups each received a different vaccine as well as a dual challenge. The remaining 2 groups were used as controls, 1 of which also received a dual challenge. Two of the 4 groups of pigs were administered 2 monovalent vaccines (designated as either monovalent vaccine A or B) of PCV2 at 7 days old and of *M. hyopneumoniae* at 21 days old. The remaining 2 vaccinated groups of pigs received a bivalent vaccine (designated as either bivalent vaccine A or B) of PCV2 and *M. hyopneumoniae* at 21 days old. All 4 vaccinated groups were challenged with *M. hyopneumoniae* at 42 days old [–14 d post-challenge (dpc)], followed by a PCV2d challenge at

Corrections:

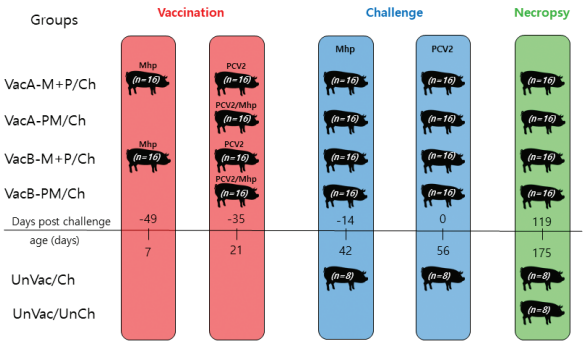
Abstract

2 monovalent vaccines (designated as either monovalent vaccine A or B) of *M. hyopneumoniae* at 7 days old and PCV2 at 21 days old, or *M. hyopneumoniae* and PCV2 at 21 days old.

Résumé

deux vaccins monovalents (identifié soit comme vaccin monovalent A ou B) de *M. hyopneumoniae* à 7 jours d'âge et PCV2 à 21 jours d'âge, ou *M. hyopneumoniae* et PCV2 à 21 jours d'âge.

Original Figure 1



New Figure 1

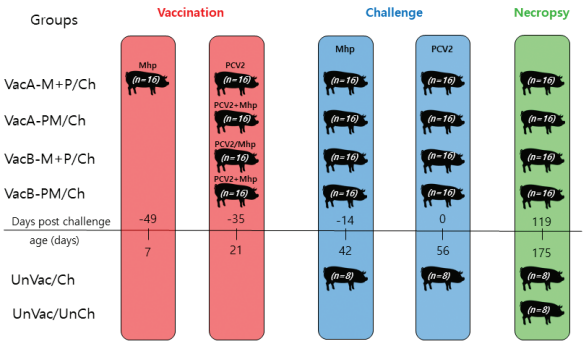


Figure 1. Experimental design. Pigs were administered a vaccine against *M. hyopneumoniae* (Mhp) and/or porcine circovirus type 2 (PCV2) and challenged with *M. hyopneumoniae* and PCV2 on certain days as shown. A number of pigs were necropsied as shown.