Making sense of atopic dermatitis

Examining the pathogenesis and diagnosis of a difficult-to-treat disease.

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Pruritus, the itching sensation that provokes scratching, is one of the most common clinical signs veterinarians see in patients. At Banfield, 20 percent of canine Pets received diagnoses in the dermatology category; 2 percent to 3 percent of all dogs examined are ultimately diagnosed with canine atopic dermatitis. When you encounter a problem this frequently, it is natural to become complacent, treating every case as routine. But these cases can be seen as diagnostic and therapeutic challenges, giving you the opportunity to communicate your skill as a diagnostician and Pet advocate to the client. Most importantly, your thorough assessment and recommendations for state-of-the-art treatments will enhance the Pet's quality of life and the human-Pet bond.

This article examines the most recent thoughts on the pathogenesis and diagnosis of canine atopic dermatitis, including serum allergy testing.

Pathogenesis

Canine atopic dermatitis has traditionally been described as a pruritic skin disease caused by a genetic predisposition to a Type 1 (immediate), immunoglobulin E (IgE)-mediated hypersensitivity reaction to environmental allergens. These allergens are typically components of house dust mites, pollens and mold spores. Most patients are allergic to multiple allergens, which are typically difficult to eliminate or avoid in the Pet's environment. Once the atopic patient produces allergen-specific IgE, it binds to mast cells in the dermis. Subsequent exposure to the allergen causes cross-linking of the bound IgE molecules, initiating mast cell degranulation. The release of inflammatory mediators (histamine, leukotrienes and substance P) results in a cascade of inflammation and the development of pruritus. During the past 10 years, it has become increasingly clear that the pathogenesis of canine atopic dermatitis is much more involved than a Type 1 hypersensitivity reaction alone. Recent studies have elucidated the important contribution of epidermal barrier defects, *Malassezia* yeast, *Staphylococcus* bacteria and T-cell mediated responses.

While it was once considered likely that

allergens gained access to the skin via inhalation, percutaneous absorption of allergens is now thought to be the primary route of exposure.[1] Thus, a defective stratum corneum, the skin's outermost protective layer, may allow greater allergenic exposure.[2] This may occur as a result of abnormal epidermal lipids or subsequent to skin trauma. To address these changes, select topical therapy designed to protect and restore the barrier function of the skin, including emollients and humectants (see *Treatment of canine atopic dermatitis*, page 38). In addition to the epidermis' protective function, we now understand the importance of epidermal dendritic cells, which capture allergens for presentation to T cells. A regular bathing routine (every seven to 14 days) should be incorporated into the atopic Pet's treatment plan, removing allergens from the skin and coat before this occurs.

The first signs of canine atopic dermatitis typically occur between 6 months and 3 years of age; however, the condition can present in older and younger Pets as well.

The yeast *Malassezia pachydermatis* is now recognized as a major contributor to the pathogenesis of atopic dermatitis. Atopic Pets frequently have an increased amount of yeast on their skin surface. *Malassezia* organisms produce a number of inflammatory substances. In addition, IgE directed against *Malassezia* antigens is more abundant in the serum of atopic dogs than nonatopic dogs.[3] Skin sensitivity to *Malassezia* extract can be transferred from atopic to normal dogs via serum (the Prausnitz-Küstner test).[4] Thus, the organism itself may perpetuate atopic dermatitis, in part accounting for the substantial benefit often seen when topical and systemic products effective against *Malassezia* are prescribed for atopic Pets.

Staphylococcus intermedius infections commonly occur in dogs with atopic dermatitis. It has recently been shown that *S. intermedius* adheres more strongly to the corneocytes, the dead keratin-filled squamous cells in the stratum corneum, of atopic dogs than to those of normal dogs.[5] In humans with atopic dermatitis, it is clear that Staphylococcal exotoxins (protein A, peptidoglycans and teichoic acid) contribute to the inflammation. A similar situation is postulated in canine atopic dermatitis.[6]

The role of cytokines in the pathogenesis of atopic dermatitis is an area of active investigation. Specific cytokines are characteristic of different T helper cell subsets. Th1 cells function primarily in the regulation of phagocytosis, while Th2 cells function in IgE-mediated immune responses. In humans with acute atopic dermatitis, Th2-type cytokines (IL-4, IL-5, IL-13) predominate, whereas Th1-type cytokines (IL-2, IL-12, IFN-γ) predominate in the skin of chronic atopic dermatitis patients. Similar differences have now been reported in dogs.[7] These dynamic changes may explain why we often observe that chronic atopic Pets become less seasonal (despite static pollen seasons), are more severely affected, and display poor skin test reactivity as they age.

Clinical signs

The first signs of canine atopic dermatitis typically occur between 6 months and 3 years of age; however, the condition can present in older and younger Pets as well.[8] At Banfield, the mean age of the first recorded diagnosis of atopic dermatitis is 4.5 years.

Depending on the offending allergens and the local climate, the signs of atopic dermatitis may occur seasonally or perennially.

Perhaps this difference reflects the gradual onset of canine atopic dermatitis and subsequent delay in seeking care by many Pet owners. Alternatively, it may reflect differences in Pet populations seen in general versus specialty dermatology practice settings. Previous studies on breed prevalence and relative risk are few and relatively small compared with the one presented in the DataSavant article (*Table 2,* page 20). West Highland White Terriers are the most at-risk breed in the Banfield population, consistent with previous studies. As reported in the DataSavant article (page 17), there is a significant predilection for atopic dermatitis in neutered Pets and a slight predilection for the disease in male Pets within the Banfield population. Conflicting results on sex predilections have been obtained in studies conducted on smaller populations.

Depending on the offending allergens and the local climate, the signs of atopic dermatitis may occur seasonally or perennially. When perennial, signs may still fluctuate seasonally. Most seasonally affected Pets' signs will worsen in the spring and summer, but a smaller percentage will worsen in the winter. At Banfield, Pets are diagnosed with canine atopic dermatitis for the first time most frequently in the months of August, September and October, and least frequently in December and February (Data Savant, *FIgure 2,* page 21). These data should be interpreted in light of possible confounding variables, such as delays in seeking veterinary care, miscoding of diagnoses and seasonal consumer spending habits.

The hallmark of canine atopic dermatitis is pruritus, manifested as scratching, rubbing, chewing or licking. Erythema may represent a primary skin lesion, but alopecia, salivary staining, excoriations, papules, pustules and crusts are secondary to self-trauma or infection (*Figure 1,* page 29). The sites most frequently affected are the paws, face, ears and ventrum (*Figures 2* and *3,* page 29). Care should be taken to routinely and thoroughly examine these regions, as the client may not call your attention to them (*Figure 4,* page 29). In some cases, the pruritus and lesions are generalized or involve the dorsum or perineum. Chronically affected Pets may develop lichenification and hyperpigmentation (*Figure 5,* page 29). Otitis externa *(Figure 6,* page 29) affects as many as 86 percent of dogs with atopic dermatitis at some time in the course of their disease.[8] Less frequent manifestations of atopic dermatitis include hyperhidrosis (excessive sweating), seborrhea,

Figure 1

Periocular alopecia, erythema and excoriations secondary to canine atopic dermatitis.

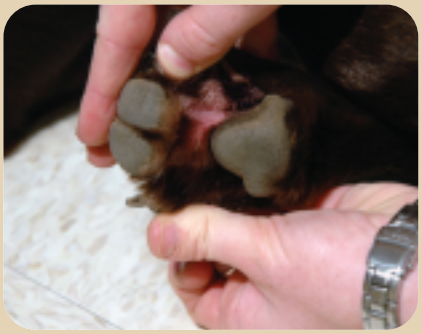
Figure 2

The paws and legs are commonly affected in atopic Pets.

Figure 3

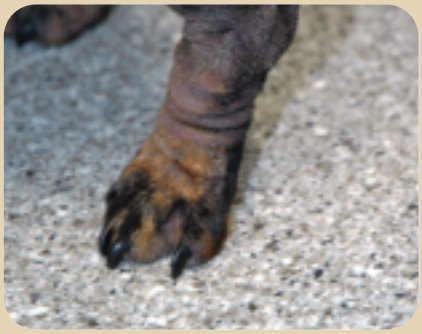
The face, ears, paws and ventrum are most often affected in canine atopic dermatitis.

Figure 4



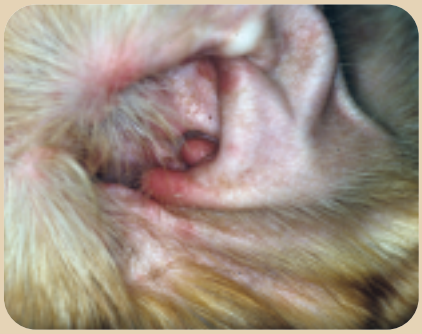
Take care to inspect the interdigital spaces as part of a thorough dermatologic examination.

Figure 5



Chronic lichenification and hyperpigmentation changes can be prevented with early intervention and consistent management.

Figure 6



Otitis externa is a common complication of canine atopic dermatitis.

paronychia (inflammation of the nail fold), acral lick dermatitis, pyotraumatic dermatitis and conjunctivitis. Many suffer recurrent episodes of superficial Staphylococcal pyoderma and/or *Malassezia* dermatitis.

Reaching the diagnosis

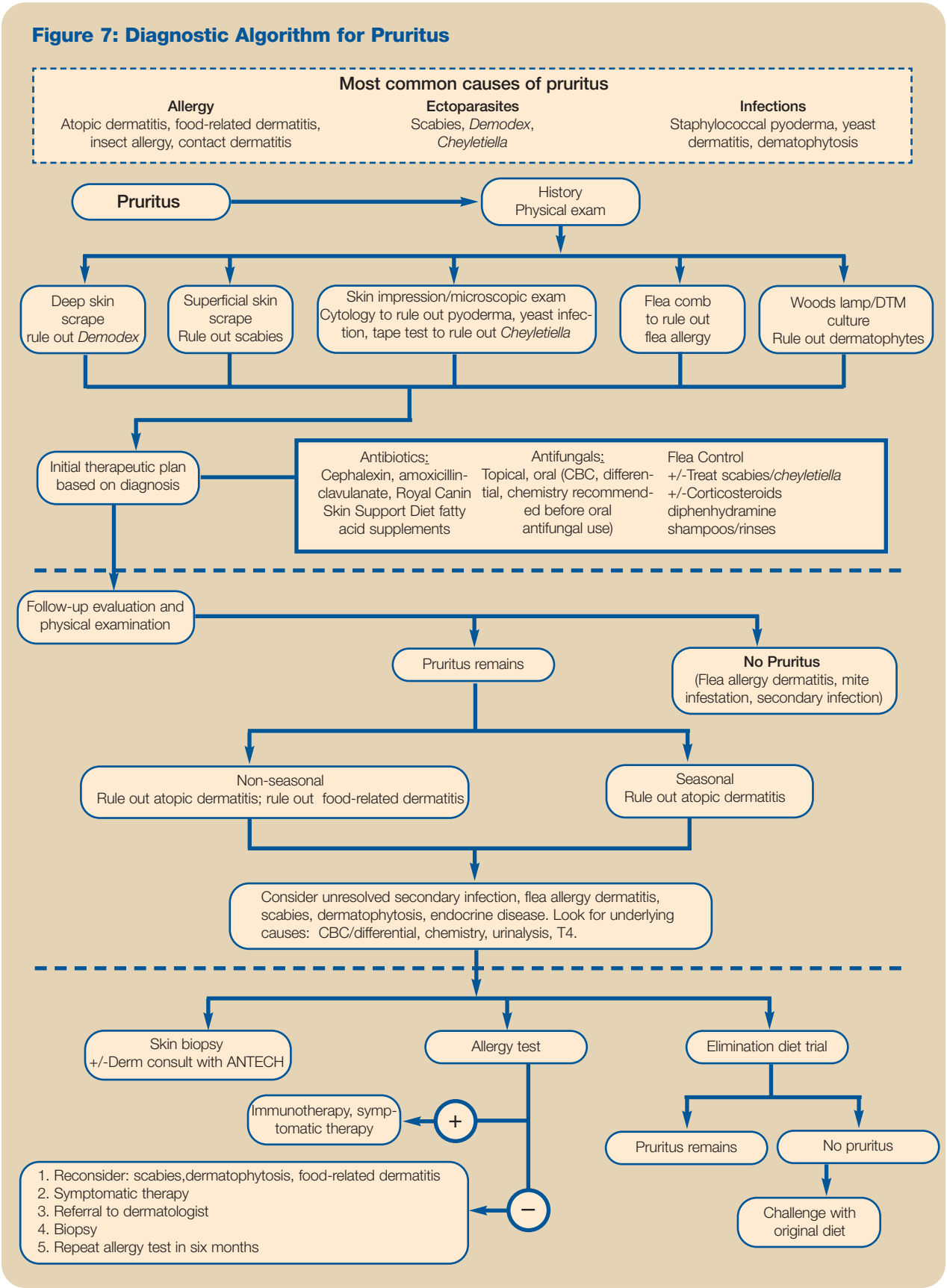
Atopic dermatitis is a clinical diagnosis, established on compatible signalment, history and clinical findings, as well as ruling out plausible alternative diagnoses (*Figure 7,* page 33, diagnostic algorithm for pruritus). It would be a straightforward diagnosis if one could simply perform an allergy test. Unfortunately, neither intradermal allergy testing (*Figure 8,* page 34) nor serum allergen-specific IgE testing is specific enough to rely upon for making the diagnosis. Furthermore, the reliability of serum allergy testing varies with different companies.[9] False-positive reactions occur with both testing methods. Allergy testing should be used to select allergens for immunotherapy prescriptions, not to diagnose atopic dermatitis.

Differential diagnoses

Following the algorithm *(Figure 7,* page 33) one can systematically rule out differential diagnoses. History, examination findings and clinical judgment will help you prioritize the differentials and diagnostic procedures in a logical manner.

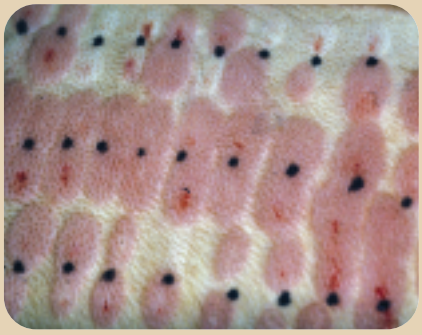
Flea-bite hypersensitivity is the only pruritic dermatopathy more common than atopic dermatitis. Both diseases may occur concurrently. Lesions vary from scale and alopecia to crusts and excoriations. Erythema and papules are common. The typical distribution over the rump and caudal thighs is familiar, but less commonly the legs and ventrum are affected. Use a flea comb to demonstrate the presence of fleas or flea excrement, but do not over-interpret the

Figure 7: Diagnostic Algorithm for Pruritus



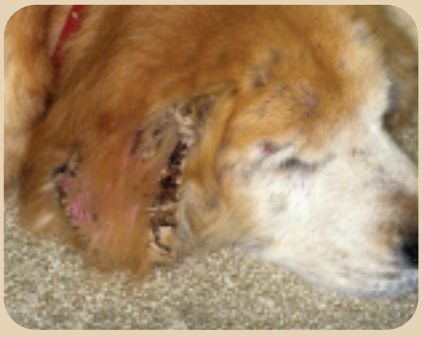
failure to find any, especially in a Pet not receiving regular flea preventive. If you practice in a region with fleas, adequate flea protection should be addressed every time the Pet is presented for pruritus.

Figure 8



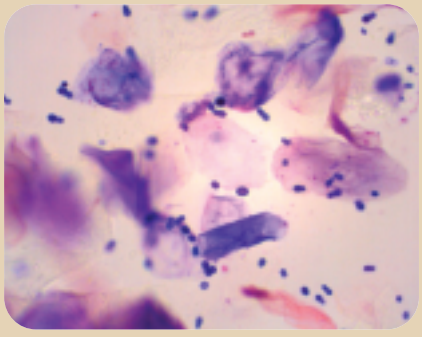
An intradermal allergy test with numerous positive reactions.

Figure 9



Crusting of the pinnal margin is suggestive of sarcoptic mange.

Figure 10



Numerous *Malassezia* organisms are evident on a cutaneous cytology sample of an atopic Pet.

Adverse food reaction may occur alone or concurrently with atopic dermatitis. A perennially pruritic Pet is more likely to suffer from adverse food reaction or atopic dermatitis due to indoor allergens than a seasonally pruritic Pet. Of course, seasonality is a less discriminating criterion in subtropical climates. The cutaneous lesions of adverse food reaction and their distribution are identical to those of atopic dermatitis. A minority of patients with adverse food reaction will have concurrent gastrointestinal signs such as soft or frequent stools. Elimination diet trials are the only reliable means to diagnose adverse food reaction. A novel protein diet, such as Royal CANIN Potato and Duck Formula™, is fed exclusively for eight weeks. If a positive response is noted, a dietary challenge, using the Pet's original food, is performed to confirm the diagnosis of adverse food reaction.

Sarcoptic mange should be considered in any pruritic dog, but especially those that have been implicated in a zoonosis, had exposure to other dogs, or have the classic lesion distribution of ear margins, lateral elbows, hocks and ventrum. Lesions vary from alopecia and papules to severe erythema, excoriations, and thick crusts (*Figure 9*), depending on the duration of the infestation. *Sarcoptes scabiei* mites are usually scarce, even on severely affected patients. Superficial skin scrapings covering broad areas increase the probability of detecting mites. If the history or physical examination findings suggest a significant (10 percent or higher) likelihood of sarcoptic mange, a therapeutic trial is recommended.

Cheyletiellosis causes mild to moderate pruritus and scaling over the dorsum. These mites are more readily detected than *Sarcoptes* mites. Because they are surface

dwellers, cellophane tape impressions or superficial skin scrapings are appropriate. Their eggs may be found attached to hairs, similar to louse nits, but about one third as large.

Demodicosis and dermatophytosis are usually not very pruritic, but may be in some cases. In generalized demodicosis, the feet may be affected and result in swelling, pain and pruritus. In some cases of dermatophytosis, particularly generalized *Trichophyton* infections, pruritus can be severe. Deep skin scrapings and Dermatophyte Test Media (DTM) fungal cultures should be performed to rule out these possibilities early in the workup of a pruritic Pet.

***Malassezia* dermatitis and Staphylococcal pyoderma** commonly contribute to the clinical lesions of Pets with canine atopic dermatitis. A thorough workup of the pruritic Pet will include skin impression cytology to assess the abundance of these microorganisms (*Figure 10,* page 34). Otic cytology should also be recommended for the pruritic Pet when otitis externa is noted. To best detect cutaneous *Malassezia* organisms, make direct slide impressions of greasy areas and use a tape-strip technique of dry, scaly lesions. Pustules and borders of epidermal collarettes are excellent areas to sample when evaluating for *Staphylococcal* pyoderma. Given the increasing concern and public awareness of antibiotic-resistant *Staphylococcus* infections, perhaps we should consider performing culture and sensitivity testing on Pets with pyoderma more often.

In most cases, the diagnostic tests described up to this point will be sufficient to make a diagnosis. Of course, there are exceptions. When you encounter one of these, blood work and a skin biopsy are recommended. A complete blood count (CBC), manual white blood cell (WBC) differential, serum chemistry screen, urinalysis, and total T4 level will help uncover the uncommon metabolic or hormonal diseases associated with pruritus. A skin biopsy may support your diagnosis of canine atopic dermatitis or uncover something unusual such as epitheliotropic lymphoma. Also known as mycosis fungoides, epitheliotropic lymphoma may present as generalized pruritus and erythema. A Pet without a history of chronic dermatitis that develops pruritus at an older age should raise your index of suspicion for this disease.

Prognosis and client education

Clients often ask you if their Pets will "outgrow" their allergies. Advise them that, in most cases, atopic dermatitis progressively becomes more severe. However, there is reason to believe that early intervention and control of inflammation may slow the progression of atopic dermatitis.[10] A well-managed Pet is healthier, happier and less likely to incur costly flare-ups. Discuss the Pet's immediate needs and the advantages and disadvantages of various long-term treatment options with the owner. Some form of topical therapy is nearly always indicated. Antihistamines and essential fatty acid supplementation may be suitable for milder cases, while glucocorticoids or cyclosporine are appropriate for moderate to severe pruritus due to atopic dermatitis. For Pets that respond poorly to or cannot tolerate these modalities, consider serum allergy testing and immunotherapy as an alternative. An informed client who understands the chronic nature of atopic dermatitis, agrees with your recommendations, and takes ownership of the therapeutic choices will be most able to successfully manage this chronic disease.

References

1. Marsella R, Nicklin C, Lopez J. Studies on the role of routes of allergen exposure in high IgE-producing beagle dogs sensitized to house dust mites. *Vet Dermatol* 2006; 17:306-312.

2. Marsella R. Atopy: New targets and new therapies. *Vet Clin North Am Small Anim Pract* 2006; 36:161-174.

3. Morris DO, Olivier NB, Rosser EJ. Type-1 hypersensitivity reactions to *Malassezia pachydermatis* extracts in atopic dogs. *Am J Vet Res* 1998; 59:836-841.

4. Morris DO, DeBoer DJ. Evaluation of serum obtained from atopic dogs with dermatitis attributable to *Malassezia pachydermatis* for passive transfer of immediate hypersensitivity to that organism. *Am J Vet Res* 2003; 64:262-266.

5. McEwan NA, Mellor D, Kalna G. Adherence by *Staphylococcus intermedius* to canine corneocytes: A preliminary study comparing noninflamed and inflamed atopic canine skin. *Vet Dermatol* 2006; 17:151-154.

6. DeBoer DJ, Marsella R. The ACVD task force on canine atopic dermatitis (xii): The relationship of cutaneous infections to the pathogenesis and clinical course of canine atopic dermatitis. *Vet Immunol Immunopathol* 2001;81: 239-249.

7. Griffin CE, DeBoer DJ. The ACVD task force on canine atopic dermatitis (xiv): Clinical manifestations of canine atopic dermatitis. *Vet Immunol Immunopathol* 2001;81: 255-269.

8. Muller GH, Kirk RW, Scott DW, Miller WH, Griffin CE. *Muller & Kirk's Small Animal Dermatology,* 6th ed. Philadelphia: W.B. Saunders, 2001.

9. DeBoer DJ, Verbrugge MJ. Results of canine serum allergen-specific IgE determinations performed by commercial laboratories on canine IgE-free samples and on samples from nonallergic dogs in: 20th Proceedings of the North American Veterinary Dermatology Forum Sarasota, Fla. 2005:191.

10. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immuno*l 2003; 112:S118-127.

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