

Review Article

Update on pathogenesis, diagnosis, and treatment of atopic dermatitis in dogs

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Improved understanding of the pathogenesis of atopic dermatitis in dogs has led to more effective treatment plans, including skin barrier repair and new targeted treatments for management of allergy-associated itch and inflammation. The intent of this review article is to provide an update on the etiologic rationale behind current recommendations that emphasize a multimodal approach for the management of atopic dermatitis in dogs. Increasing knowledge of this complex disease process will help direct future treatment options.

Atopic dermatitis in dogs is a common inherited chronic inflammatory skin disease involving abnormalities in skin barrier function and cutaneous inflammation, secondary staphylococcal and *Malassezia* skin and ear infections, and hypersensitivity to environmental allergens, food allergens, or staphylococcal or *Malassezia* allergens (or both pathogens).¹⁻³ For some dogs that have clinical signs compatible with atopic dermatitis, the results of intradermal or serum environmental allergen testing are negative; in those cases, the term atopic-like dermatitis has been used to describe the disease. It is possible that dogs with atopic-like dermatitis are allergic to minor allergens that are not included in the environmental allergen tests or that their immune dysregulation does not involve the production or antigen-binding function of IgE.

Atopic dermatitis is relentlessly progressive, and early intervention and control are needed to slow the disease process and provide affected dogs with a decent quality of life. The constant scratching and secondary infections associated with atopic dermatitis can greatly strain the bond between affected dogs and their owners to a point where the dogs may be relinquished to rescue shelters or euthanized. In canine

cases of atopic dermatitis, good communication and frequent contact with owners by all members of the veterinary team along with appropriate owner education are crucial for successful disease control.

The pathogenesis of atopic dermatitis is complex. It is likely that a defective skin barrier allows microbial adherence, penetration of allergenic proteins, and initiation of abnormal inflammatory and allergic responses. Initially, the immune response is dominated by T_H2 cells and involves cytokines such as IL-4, IL-5, IL-6, IL-13, and IL-31.^{1,4} Development of chronic inflammation, however, involves a mix of T_H1, T_H2, T_H17, and T_H22-cell mediators.⁴ Although many veterinarians are familiar with the difference between T_H1 and T_H2 cells, it is important to realize that there are other subsets of T_H lymphocytes.⁴ These cell subsets help mediate specific effector functions that develop in response to antigen-presenting cells. In general, T_H1 cells protect against intracellular pathogens (eg, viruses) and participate in cancer surveillance. The T_H2 cells support antibody production and immunoglobulin class switching. Also, T_H2 cells protect against multicellular parasites through their ability to activate the production of IgE and to activate eosinophils; T_H2 cells can be coopted for the mediation of allergic disease. The T_H17 cells are critical for neutrophil effector function, and this cell subset is believed to protect against extracellular pathogens, particularly at epithelial surfaces. The T_H22 cells promote and regulate tissue inflammation and repair; they are believed to promote epithelial proliferation in the skin.⁴

ABBREVIATIONS

IL	Interleukin
JAK	Janus kinase
mAb	Monoclonal antibody
PAR2	Protease-activated receptor 2
T _H	Helper T
TSLP	Thymic stromal lymphopoietin

Atopic dermatitis has characteristic historic and clinical features, although the distribution of lesions and the clinical signs vary among individual dogs and dog breeds. A key feature of the disease is pruritus, which is the most common reason that owners bring their dogs to veterinarians. No diagnostic test exists for this disease. The diagnosis depends on the history and clinical signs (**Figure 1**) and ruling out other possible causes of itch.³ The most recent set of diagnostic criteria for atopic dermatitis that have been developed include initial itching without lesions in young dogs (≤ 3 years old), an indoor lifestyle, affected feet and concave aspects of the pinnae, and initial responsiveness to glucocorticoid administration.³ Unless the dog has concomitant flea allergy dermatitis or scabies, the caudal region of the dorsum and ear margins are not affected.

A 4-step approach to facilitate identification of underlying diseases in dogs with pruritus and the common flare factors in atopic dermatitis has been proposed.^a To reach a diagnosis of atopic dermatitis, curable underlying causes of itching should be ruled out or treatment administered; the 4 main causes of pruritus (in order of treatment difficulty) are parasitic infestations, pyoderma or yeast infections, food allergy, and atopic dermatitis. Conditions caused by ectoparasites and cutaneous infections are fairly easily treated and typically resolve. In most parts of the world, fleas and *Sarcoptes scabiei* infestations are most important; however, in some geographic regions, infestations with other biting insects, mites, and lice should be considered. Staphylococcal pyoderma and yeast infections caused by *Malassezia* spp are the most common infections of the skin and ears that require management. Food allergy should be considered for dogs with nonseasonal itching in the presence or absence of gastrointestinal tract signs. Treatment and control of ectoparasitic infestations and skin infections will allow assessment of any unresolved itching. Carefully evaluated food trials should be performed for dogs with nonseasonal pruritus. Pure food allergy, wherein all the clinical signs

are controlled by diet alone, is uncommon in dogs. More commonly, food can be one of the triggers for the itching and inflammation in atopic dogs (leading to food-induced atopic dermatitis). Having ruled out or eliminated other potential causes, a diagnosis of atopic dermatitis can be made.

A lifelong management plan for affected dogs must be developed because atopic dermatitis is not curable. The management plan needs to be tailored to each dog and pet owner. The goals of treatment are to maximize the quality of life for the pet and for the caregiver, to support and protect the human-animal bond, and to decrease allergy flares while minimizing the cost and adverse effects of medication and complexity of treatment regimens. Treatment guidelines for the effective management of atopic dermatitis have been established.⁵⁻⁷

Genomic studies in dogs with atopic dermatitis

The clinical signs of atopic dermatitis in dogs and humans reflect a complex interaction between the patient's genetic characteristics and the patient's environment. The clinical signs and responses to treatment can vary among human patients, among individual dogs of the same breed, and among dog breeds.^{8,9} There are over 30 genes involved in the pathogenesis of the human disease¹⁰ that affect innate and adaptive immune responses as well as the development and maintenance of the skin barrier. Through genotyping clinical subsets of atopic dermatitis, improvements in diagnostic testing and the ability to predict responses to individual therapeutic agents are being made.

Strong breed associations support a genetic basis for atopic dermatitis in dogs, although the predilection varies among regions.¹¹ Mean heritability in British guide dogs (Labrador Retrievers and Golden Retrievers) is 0.47, indicating that nearly 50% of the risk of developing atopic dermatitis is determined by an individual's genotype.¹² The risk is greatest when both parents have atopic dermatitis, moderate when only 1 parent is affected, and lowest when neither parent has atopic dermatitis.^{11,12} Methods to identify genetic associations include genome-wide linkage, genome-wide association, and candidate-gene association studies. Several genomic analyses of dogs with atopic dermatitis have been performed (**Appendix**).¹³⁻²³

To date, the analyses have identified candidate genes including filaggrin and those that affect lymphocyte function, that affect circulating IgE concentrations, and that affect the cytokine receptor for TSLP (a proinflammatory cytokine produced by keratinocytes). Other specific proteins that have been identified in humans with atopic dermatitis remain to be identified in dogs with atopic dermatitis. However, the



Figure 1—Photograph of a dog with chronic atopic dermatitis. Notice the distribution of lesions on the ventrum, face, and feet.

results of the genomic studies in dogs confirm the complexity of this disease.

Loss-of-function filaggrin mutations are common in humans with atopic dermatitis and appear to be involved in some, but not all, affected dog breeds. Filaggrin is a multifunctional protein present in the skin, and when abnormal, contributes to the skin barrier defect involved in the development of atopic dermatitis. Lack of filaggrin involvement might be one of the reasons for the variable disease phenotype among breeds. For example, findings of 3 genomic studies^{14,19,20} in West Highland White Terriers suggest that the gene for filaggrin is not involved in development of atopic dermatitis, whereas the filaggrin gene is associated with atopic dermatitis in Golden Retrievers. Seemingly, West Highland White Terriers with atopic dermatitis may have skin barrier defects, but those defects may involve genes that differ from those that mediate skin barrier defects in other affected dog breeds. To date, only the gene for the TSLP receptor appears to be involved in atopic dermatitis in dogs of all studied breeds. Thymic stromal lymphopoietin is a cytokine produced by keratinocytes following epidermal damage. It initiates T_H2-cell responses and stimulates itching. A change in the expression or affinity of the TSLP receptor might allow this proinflammatory cytokine to bind more tightly, thereby stimulating more inflammation. Other genes potentially involved include a protein tyrosine phosphatase that modulates T- and B-cell responses to antigens and plakophilin 2, a protein involved in epidermal adhesion. Taken together, genomic analyses are beginning to reveal the genetic underpinnings of the immune dysregulation and barrier defect identified in dogs with atopic dermatitis.

Atopic dermatitis is clearly a heritable disease, although interaction with environmental factors (eg, allergen exposure, pollutants, and urban vs rural lifestyle) also influences the disease risk and phenotype among dogs.^{11,12} New genomic techniques have the potential to allow identification of relevant gene polymorphisms associated with the disease. However, the genetic basis is complex and varies among breeds and geographic regions, even at the level of the transcription and function of a single associated gene. This complexity may explain differences in the clinical phenotype and responses to treatment of affected dogs, making it difficult to develop simple genetic diagnostic tests for atopic dermatitis. Nevertheless, advances in bioinformatics should help link certain genotypes and clinical phenotypes. Predictive algorithms could then be used to identify dogs at risk of developing atopic dermatitis, select interventions to prevent disease development, design effective treatment programs, and predict the likelihood of success or risk of adverse effects associated with different treatments. However, selective breeding programs that avoid propagation by dogs with atopic dermatitis must be undertaken carefully to prevent inadvertent selection for other deleterious traits, particularly if the gene pool is restricted. Although genomic analysis for atopic dermatitis in dogs is in its early stages, it

will undoubtedly contribute to diagnostic approaches and treatment options in the future.

Skin microbiota in dogs with atopic dermatitis

Dogs with atopic dermatitis are predisposed to recurrent staphylococcal and *Malassezia* infections in the skin and ears.²⁴ Staphylococci and *Malassezia* organisms can stimulate the release of pruritogenic and inflammatory cytokines from skin cells.²⁴ Those microbes also produce conventional allergens that result in IgE-mediated mast cell degranulation, superantigen-induced clonal T-cell activation, and protease-associated damage of the skin barrier.^{25–27} A complete understanding of all the organisms on the skin has recently become critical. The skin microbiota includes all microorganisms and their genetic material living on the skin; interactions between the microbiota and the host affect the pathogenesis of atopic dermatitis in humans and dogs.^{24,28,29} The commensal microflora are vital for health; they can prevent pathogen invasion and interact with the innate and adaptive immune system to induce tolerance to harmless environmental stimuli. Loss of biodiversity in the microbiota of the skin and gastrointestinal tract has been linked to the development of chronic inflammatory and allergic diseases in dogs, mice, and humans.

Compared with healthy dogs, there is decreased biodiversity among the cutaneous microbiota with a notable increase in the number of staphylococci in dogs with atopic dermatitis.^{30–34} Low-grade inflammation may be a selection factor that favors more pathogenic bacteria and decreases the survival of harmless resident bacteria on the skin. Sensitized dogs challenged topically with allergen have a higher number and proportion of staphylococci, relative to other bacteria, and reduced diversity among cutaneous microorganisms at the site of the challenge.³³ The proportion of staphylococci appears to correlate with disease severity.^{32,34} The response to antimicrobial treatment is complex; such treatment does not eliminate all bacteria, but it restores bacterial diversity by decreasing the population of staphylococci and improving skin barrier function.³³ The interactions among the immune system, microbiota, and skin barrier warrant much more study, with the potential to generate new ideas regarding treatment for atopic dermatitis and antimicrobial stewardship.

Targeting T_H2 cell-associated cytokines to control allergic itch and inflammation

Dogs with atopic dermatitis, like humans with atopic dermatitis, have a dysregulated immune response. Acute itching and inflammation are associated with cytokines produced by T_H2 lymphocytes (eg, IL-4, IL-5, IL-10, IL-13, and IL-31) and by cytokines known to promote the differentiation or ac-

tivation of T_H2 lymphocytes (eg, TSLP, IL-25, and IL-33).^{1,4} Until the last decade, the only medications with proven efficacy in cases of atopic dermatitis were glucocorticoids; long-term use of glucocorticoids is associated with multiple adverse effects because glucocorticoid receptors are present in almost all cells. More recently, drugs such as cyclosporin A^b and oclacitinib^c and a caninized (ie, genetically modified to be tolerated by the targeted animal species, namely dogs) anti-canine IL-31 mAb (lokivet-mab^d) have been developed to target cytokines that drive pruritus and inflammation in dogs with allergic dermatitis, including atopic dermatitis. Recently, this mAb received an extended label from the USDA for use in any allergic dermatitis.

Cyclosporin A blocks the transcription of many pro-inflammatory genes in activated immune cells by forming a complex with cyclophilin, a cytosolic protein. The cyclosporin-cyclophilin complex inhibits the phosphatase calcineurin, which blocks dephosphorylation of the nuclear factor of activated T cells. In activated T cells, the phosphorylated nuclear factor cannot move into the nucleus to induce gene transcription. The main action of cyclosporin is to decrease T-cell activation by inhibiting IL-2 production and release. It also suppresses production of mRNA for IL-2, IL-4, and interferon- γ in stimulated canine peripheral blood mononuclear cells, inhibits mast cell and eosinophil degranulation, and depresses pro-inflammatory eicosanoid formation.³⁵⁻³⁹ Cyclosporin has been safely and effectively used for the treatment of dogs with atopic dermatitis for more than 10 years. It is given orally at 5 mg/kg (2.27 mg/lb) once daily for 4 to 6 weeks, and then treatment is tapered to the lowest dose and frequency of administration that controls the disease; the most common adverse effects of treatment are vomiting and diarrhea.

Oclacitinib inhibits the activity of cytokines that are dysregulated in cases of atopic dermatitis by selectively inhibiting certain JAKs (those most inhibitory against JAK1, compared with activities against JAK2, JAK3, or TYK2 in cell-free enzyme studies) associated with the intracellular portion of type I and type II cytokine receptors.⁴⁰ Inhibition of JAKs blocks the cytokine signal, thereby preventing gene transcription and protein production. Cytokine receptors use distinct combinations of different JAKs.^{40,41} In in vitro canine and human cell cultures, oclacitinib preferentially inhibits cytokines whose signaling is mediated by JAK1 and JAK3 (both of which are involved in itching and inflammation) over JAK2 (which is important in hematopoiesis and innate immunity). Oclacitinib inhibits the pruritogenic and pro-inflammatory activity of IL-2, IL-4, IL-6, IL-13, and IL-31 in particular. It has been approved for use in dogs $\geq$ 12 months old for control of pruritus associated with allergic skin diseases (ie, flea, food, and contact allergies) and the signs associated with atopic dermatitis. It is administered orally at a dosage of 0.4 to 0.6 mg/kg (0.18 to 0.27 mg/lb), twice daily for up to 14 days, and then once daily thereafter. Oclacitinib has been shown to be as

effective as prednisolone or cyclosporin for control of allergic skin disease-related itching. Oclacitinib inhibits pruritus more rapidly than does cyclosporin through inhibition of signaling by IL-31, a key cytokine in development of early inflammation and itching.^{4,42-46} The efficacy of oclacitinib and cyclosporin illustrates the important role of cytokines, particularly JAK-dependent cytokine-receptor complexes, in the development of pruritus and inflammation in dogs with atopic dermatitis. Efficacy of these drugs has fueled interest in evaluating alternative approaches to inhibition of cytokine function in dogs with atopic dermatitis.

Monoclonal antibodies are a distinct class of therapeutic agents that differ from traditional pharmaceuticals, which are synthesized by means of medicinal chemistry or purified from natural sources, such as bacteria or fungi. Administration of mAbs has become one of the most successful treatment options for autoimmune and other chronic inflammatory diseases in human medicine. The attractiveness of treatment with mAbs stems from their ability to combine high specificity toward their target with low off-target effects. Several mAbs have been generated to neutralize soluble factors, such as cytokines, or to bind or antagonize cell-surface receptors. Their long half-life allows production of long-acting formulations. Because antibodies are protein based, mAbs that are used in patients are designed specifically to ensure they are well tolerated by the host and do not induce an inappropriate immune response. Given the potential for mAbs to be recognized as foreign and induce hypersensitivity or other immune responses (immunogenicity), humanized mAbs should not be used in veterinary species and caninized mAbs should not be used in cats or other species.

A caninized (ie, murine antibody genetically modified to contain sequences from canine IgG) anti-canine IL-31 mAb^d has been developed to neutralize the effects of canine IL-31.⁴⁷ Interleukin-31 induces pruritus in various species, including rodents, dogs, and non-human primates,⁴²⁻⁴⁶ and pro-inflammatory mediator production from immune cells and skin cells.⁴⁸ It has been confirmed as a key cytokine in the development of early skin lesions of dogs with atopic dermatitis.⁴⁴ The anti-canine IL-31 mAb effectively controls pruritus and ameliorates skin lesions in dogs with atopic dermatitis⁴⁷ and has been approved by the USDA and the European Medicines Agency for aiding in the reduction of clinical signs associated with atopic dermatitis and other allergic skin diseases in dogs. It is administered at a dosage of 2 mg/kg (0.91 mg/lb), SC, every 4 to 8 weeks (in the United States) or 1 mg/kg (0.45 mg/lb), SC, every 4 weeks (in the European Union). Additional anti-cytokine approaches are still under investigation in veterinary medicine, and products of interest include an anti-TSLP vaccine; anti-TNF- α , anti-IL-17A, and anti-IL4R α mAbs that neutralize their respective cytokines or cytokine receptors^{48,49}; and a chemoattractant receptor T_H2 (a prostaglandin D2 receptor) antagonist that is believed to reduce cytokine production from immune cells. Other approaches target B-cell (an-

ti-CD20 [CD20 being a surface marker on activated B lymphocytes]) or mast cell functions (anti-IgE mAbs or c-kit [receptor tyrosine kinase] inhibitors).

The complex pathogenesis and variability in clinical signs of atopic dermatitis provide a large number of potential therapeutic targets for small molecule drugs and mAbs. Future approaches to diagnosis and monitoring response to treatment could include the detection and quantitation of circulating serum biomarkers (eg, IL-31 and other cytokines). It is possible that, in the future, clinicians could use a diagnostic test panel to identify the subtype of atopic dermatitis in individual dogs and apply that information to design a customized treatment plan. The genomic studies that have been undertaken to date represent first steps toward those goals.

A critical role for the skin barrier

The evidence to support the importance of skin barrier dysfunction in the pathogenesis of atopic dermatitis in dogs continues to accumulate.²⁴ The skin barrier is comprised of corneocytes of the stratum corneum surrounded by organized lamellae of lipids containing cholesterol and its esters, free fatty acids, and ceramides.²⁴ A healthy barrier keeps the skin hydrated and prevents skin penetration by allergenic and microbial proteins. Decreased amounts of ceramides and altered expression and distribution of filaggrin, compared with findings in the skin of healthy dogs, along with ultrastructural defects in the stratum corneum are indicative of a barrier defect in dogs with atopic dermatitis.²⁴ The disrupted skin barrier allows allergens, irritants, and other triggers to penetrate the skin and activate immune responses. The skin barrier defect is also associated with dysbiosis (imbalance in the skin microbiota).^{24,50}

Although a primary genetic barrier defect may be present in some breeds (Appendix), T_H2-cell cytokine-dominated inflammation further worsens the barrier defect and may induce a barrier defect in dogs without an identifiable genetic predisposition.⁵⁰⁻⁵⁵ Increased allergen penetration of the skin facilitates uptake, processing, and presentation of the allergen as major histocompatibility complex class II peptides by Langerhans cells, which further promotes the T_H2-cell response, thereby leading to a vicious cycle of inflammation and sensitization to multiple allergens.⁵¹ In an experimental model of atopic dermatitis in dogs, removal of the stratum corneum by tape stripping enhanced expression of surface molecules (eg, major histocompatibility complex class II, CD86, CD40, CD54, and CD11c) on Langerhans cells and promoted allergic sensitization.⁵² Self-trauma and damage of the skin barrier trigger the release of epidermal TSLP, which polarizes skin dendritic cells to stimulate a T_H2-cell response.⁵⁰⁻⁵⁵

Compared with expression of TSLP in dogs without atopic dermatitis, dogs with atopic dermatitis have increased TSLP expression.^{55,56} The patterns of expression for TSLP and for PAR2 following epicutaneous challenge with house dust mites in dogs with

atopic dermatitis differ from those in healthy dogs.⁵⁶ The proteolytic activity of house dust mite allergens is able to activate PAR2 and impair the skin barrier by reducing expression of stratum corneum adhesion proteins, such as corneodesmosin and claudin-1.⁵⁷ The expression of tight junction proteins is also decreased by PAR2, which results in further degradation of the skin barrier.⁵⁸ Decreased expression of several tight junction proteins in lesional and non-lesional skin of dogs with experimentally induced atopic dermatitis has been reported.^{59,60} Skin barrier impairment in dogs with atopic dermatitis may therefore be induced by a wider range of molecules than only ceramides or filaggrin.

Currently, administration of both oral and topical lipid supplements to repair the skin barrier is advocated for dogs with atopic dermatitis.^{6,7} Nutrition has an important effect on skin health in general and on skin barrier function in particular. In dogs, nutrients such as essential fatty acids, pantothenate, choline, nicotinamide, histidine, and inositol have proven beneficial effects on skin barrier function.⁶¹ Feeding of diets enriched in these 6 nutrients may reduce the risk for development of atopic dermatitis in dogs if provided early in life; on the basis of owner assessment, the proportion of Labrador Retriever puppies that developed clinical signs of atopic dermatitis was significantly lower among dogs that were fed a supplemented diet (2/24 dogs), compared with that among dogs that were fed a traditional diet (10/33 dogs).⁶² Although that study⁶² did not directly assess effects on skin barrier function, the investigators speculated that the benefit may be linked to decreased allergen penetration attributable to improved barrier function.

Oral administration of essential fatty acids to dogs with atopic dermatitis increases the overall lipid content of the stratum corneum, and the composition and ultrastructure of the stratum corneum become more similar to those of healthy dogs.⁶³⁻⁶⁷ Oral treatment with essential fatty acids may decrease skin sensitivity and improve skin barrier function and condition, but there is insufficient evidence to recommend their long-term use as monotherapy.

A recently investigated strategy for the treatment of atopic dermatitis in dogs is the topical application of lipid emulsions for skin barrier repair. Phytosphingosine, a long-chain, complex fatty alcohol that is a water-binding agent, has been used in veterinary medical preparations (shampoos, sprays, mousses, and spot-ons[®]) as an aid in skin barrier repair. Phytosphingosine is a ceramide precursor, and it is hypothesized (but not yet proven) that topical application increases ceramide concentration in the skin. Results of 2 pilot studies^{68,69} have indicated that topical preparations containing phytosphingosine increase the thickness and improve the organization of the stratum corneum lipid bilayer. However, improvements in skin hydration and ceramide concentration were not observed, and further work is needed to determine whether ceramide production by keratinocytes is increased and skin hydration is improved with application of phytosphingosine over a longer period.

The uses of other lipid-based topical formulations in dogs with atopic dermatitis have been evaluated. Topical application of a product^f containing ceramides, free fatty acids, and cholesterol was shown to improve the ultrastructure of the stratum corneum, increase the number of lipid lamellae and normalize the types of lipid in the stratum corneum, and decrease severity of atopic dermatitis in affected dogs.⁶⁸⁻⁷² A plant oil extract mixture^g may also be effective; 8 weekly treatments with the mixture in a spot-on formulation decreased itching scores by 25% and skin lesion scores by 39% in 24 dogs with atopic dermatitis.⁷³ The best results were seen in cases of mild to moderate atopic dermatitis when the plant oil extract mixture was used as an adjunctive treatment along with administration of allergen-specific immunotherapy, glucocorticoids, and antihistamines with or without use of medicated shampoos; however, direct effects on the skin barrier were not assessed in that study.⁷³ There are several other shampoos and sprays that contain ceramides, but the efficacy of those products has not been established.

Two new approaches to the treatment of dogs with atopic dermatitis include the topical use of synthetic pseudoceramides (which are less costly than natural ceramides) and plant extracts containing glycyrrhetic acid. Pseudoceramides have not been fully evaluated in dogs, but a topically applied lotion^h containing glycyrrhetic acid, essential fatty acids, and ceramides appeared to have some benefit in reducing itching in 14 dogs with atopic dermatitis; over the 3 months of that study,⁷⁴ no reduction in transepidermal water loss was detected.

There is a great need for effective lipid-based topical products that are specifically formulated for dogs with atopic dermatitis and that are easy to apply and well tolerated. These products must be critically evaluated for their ability to restore the skin barrier and maintain its efficacy. The ability to prevent disease in dogs through topical skin barrier repair has not been assessed but should be studied; the findings could be applicable to the prevention of atopic dermatitis in children.⁷⁵

Effective management of atopic dermatitis in dogs

Given the information available to date, the question arises as to how best to treat dogs with atopic dermatitis. Results of genomic studies indicate that the treatment approach should be adjusted for each individual dog on the basis of its breed, clinical signs, and responses to interventions. Studies of the skin microbiota suggest that the pathogen load on the skin of affected dogs should be reduced with regular topical treatments and judicious use of systemically administered broad-spectrum antimicrobials. Cytokine study data support the targeting of the cytokines that induce inflammation and itching. On the basis of the findings of skin barrier investigations, optimal nutrition and topical lipid treatments should be considered. All the accumulated information underscores the fact that atopic dermatitis is more than just

an IgE-mediated allergy-based disease. Open-access treatment guidelines for dogs with atopic dermatitis have emphasized the need for a multimodal approach that is customized for each affected dog.^{2,6,7}

For any dog with atopic dermatitis, the first step in the treatment regimen is to provide relief of pruritus and inflammation. Almost all dogs will require some form of anti-inflammatory and antipruritic treatment. In general, owners will not pursue the other aspects of multimodal treatment if their perception is that their dogs remain uncomfortable. With more targeted treatments now available, glucocorticoid administration is no longer required for the treatment of most dogs with atopic dermatitis.^{6,7,38,39,42,76-79} Cyclosporin has been used in the treatment of dogs with atopic dermatitis for over a decade with reasonable efficacy and safety. Oclacitinib, a JAK inhibitor,⁷⁶⁻⁷⁸ and a caninized anti-IL-31 mAb^{47,79} provide potential new approaches that target allergy-related cytokines, and these treatments provide substantial relief of clinical signs in dogs with atopic dermatitis. Development of those treatment options was directly related to the improved understanding of the role for cytokines in the pathogenesis of atopic dermatitis.

Controlling flare factors is essential for long-term success in the management of dogs with atopic dermatitis. Use of the described 4-step diagnostic process to identify atopic dermatitis in dogs with pruritus can also facilitate effective care and maximize treatment success. Step 1 encourages ectoparasite control. The new orally administered isoxazolines can provide excellent broad-spectrum flea, tick, and mite control, and results of recent studies^{80,81} have suggested that their use reduces itching in dogs that have not only flea allergy but also atopic dermatitis. Orally administered products are ideal for dogs with atopic dermatitis because there is no loss of efficacy associated with frequent bathing, as occurs with topical treatments. Step 2 advocates regular topical treatment to control bacterial and yeast infections. Bathing reduces the itching, odor, exudation, and crusting associated with infection. Bathing also removes allergens from the skin and provides temporary relief from pruritus; when combined with topical lipid treatments, the quality of the skin barrier can be improved as well.²⁹ High standards of antimicrobial stewardship with more frequent microbial culture and antimicrobial susceptibility testing are needed to combat the emergence of methicillin-resistant staphylococci in veterinary patients in general and provide more effective infection control for dogs with atopic dermatitis.⁸² Step 3 involves diagnosis and avoidance of food triggers, which is critical in dogs with food-induced atopic dermatitis and in dogs with both food and environmental triggers. Nutrition for dogs with atopic dermatitis should be optimal; several diets have been developed to facilitate barrier repair, but hard evidence for the superiority of any specific diet is lacking. Nevertheless, dogs with atopic dermatitis that were fed a diet enriched with essential fatty acids had reductions in itching and inflammation in the skin, compared

with the effects of a home-cooked diet fed to other affected dogs.⁸³ Step 4 leads to the diagnosis of atopic dermatitis; however, this is difficult because of the genetic nature of the disease and the inability to control exposure to many of the trigger factors, such as pollens, mites, or molds. Once a diagnosis of atopic dermatitis has been made for a given dog, treatment options need to be considered.

To date, allergen-specific immunotherapy is the only treatment for atopic dermatitis in dogs that appears to have the potential to normalize the dysregulated immune response and thereby slow the progression of the disease. However, the duration of such treatment is long, often requiring 6 to 12 months before improvement is evident; unfortunately, it is ineffective in some dogs and is only partially effective in many cases.^{6,7} Nevertheless, when effective, it can substantially reduce the need for anti-inflammatory medication over the lifetime of an affected dog. Interpretation of allergy test results requires experience and skill, and management of immunotherapy can be difficult in that frequent dosage adjustments are required for optimal outcomes. Allergen-specific immunotherapy is best performed in consultation with a board-certified dermatologist who has experience and expertise in allergy immunotherapy formulation. Treatment options include SC, sublingual, and intralymphatic routes of administration, but there is a lack of evidence regarding which approach is best. In fact, it is possible that response is dependent on the individual patient. A role for microbial hypersensitivity (to *Staphylococcus pseudintermedius*, *Malassezia* spp, or both) in dogs with atopic dermatitis has been suggested, and immunotherapy specifically against *Malassezia* organisms has been successful in some dogs with atopic dermatitis and *Malassezia* hypersensitivity.⁸⁴ It is important to realize that no 1 treatment, including any of the newer pharmacological interventions, has 100% efficacy in canine cases of atopic dermatitis. The treatment approach to each dog with atopic dermatitis must be customized and be flexible to adjust to differing needs as the patient ages.

Atopic dermatitis is a lifelong disease. As dogs with atopic dermatitis age, concomitant diseases (eg, osteoarthritis, endocrinopathies, and neoplasia) will likely develop and have to also be considered and managed. For dogs with atopic dermatitis that are refractory to standard treatment protocols or in which there has been a relapse of disease, referral to a veterinary dermatologist is always helpful. In fact, early referral may be ideal for those affected dogs who are young (eg, 1 to 2 years old) and have nonseasonal, moderate to severe disease. Optimal outcomes are more common when primary care veterinarians partner with dermatology specialists in the management of dogs with atopic dermatitis. It is best to avoid repeated, intermittent polypharmacy without a diagnosis because this can result in chronic inflammation in the skin, antimicrobial-resistant infections, and owner frustration and financial exhaustion.

Overview

With the accumulation of research data, it has become evident that atopic dermatitis in dogs is a much more complex disease than originally thought. Genomic analyses have suggested that a number of genes that affect immune function and skin development are involved and that there are differences in the genes mediating the disease among dog breeds. This genetic information provides a possible explanation for the variation in clinical signs and responses to treatment among affected dogs, and perhaps will lead to the development of predictive tests. With regard to treatment, the development of cytokine-targeted treatments has the potential for safer and more effective control of the itching and inflammation associated with this chronic disease. Most dermatologists support the use of nutrition optimized to provide the correct balance of essential fatty acids and the topical application of lipid products to improve skin and coat quality. Allergen-specific immunotherapy is still advocated as the only treatment that can modify the disease process. Allergen-specific immunotherapy has the potential to reduce the lifetime need for medication.

Atopic dermatitis takes a toll on the affected dogs, the owners, and the veterinarians who treat those dogs. First and foremost, the goal should be to provide dogs with atopic dermatitis immediate relief from clinical signs and then work toward a long-term solution. Veterinary medical personnel can help provide a better quality of life for dogs with atopic dermatitis and their caregivers through the combination of setting forth a positive and supportive team approach, following a proactive diagnostic and treatment plan, and offering owners ongoing education, communication, and follow-up.

Footnotes

- a. Rosenbaum MR. The four step approach to the itchy dog, in Proceedings. 25th Annual Atlantic City Veterinary Conference (available to registrants as a PDF or through the Veterinary Information Network).
- b. Atopica, Elanco Animal Health, Johnston, Iowa.
- c. Apoquel, Zoetis Inc, Parsippany, NJ.
- d. Cytopoint, Zoetis Inc, Parsippany, NJ.
- e. Douxo, Ceva Animal Health LLC, Lenexa, Kan.
- f. Allerderm Spot-on, Virbac, Carros, France.
- g. Dermoscent Essential 6, Laboratoire de Dermo-Cosmetique Animale (LDCA) Technopole Castres Mazamet zac Causse, 81100 Castres, France.
- h. Ribes Pet Ultraemulsion, NBF Lanes Pet Line, Milan Italy.

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Appendix

Summary of genomic analyses in dogs with atopic dermatitis.

Analysis	Dog breeds investigated	No. of dogs (affected, healthy)	Summary of findings	Candidate gene	Clinical relevance	Reference
Candidate gene association study	Pug Shih Tzu Poodle	12, 19	2 SNPs detected in filaggrin gene on chromosome CFA 17	Filaggrin	Resultant changes in protein that contribute to skin barrier	Theerawatanasirikul et al ¹³
Genome-wide linkage study	West Highland White Terrier	30, 50 (28 additional dogs whose health status could not be determined were also included)	There was no linkage between atopic dermatitis and filaggrin gene in this cohort of dogs	No genes were identified as being linked to atopic dermatitis in this cohort of dogs	No detectable abnormalities in this skin barrier protein	Salzmann et al ²³
Genome-wide association study	West Highland White Terrier	35, 25	A genomic sequence of 1.3 Mb on chromosome CFA 17 was associated with dogs with atopic dermatitis. The skin barrier protein filaggrin was not associated with atopic dermatitis in this cohort. Protein tyrosine phosphatase nonreceptor-type 22 was implicated in dogs with atopic dermatitis	Protein tyrosine phosphatase	Effects on function of T and B lymphocytes in response to antigen	Roque et al ^{21,22}
Genome-wide association study and haplotype analysis	West Highland White Terrier	49, 30	There was no association of filaggrin with atopic dermatitis in this cohort		No detectable abnormalities in this skin barrier protein	Barros Roque et al ¹⁴
Genomic sequencing	West Highland White Terrier	3, 3	Protein tyrosine phosphatase nonreceptor-type 22 is important in lymphocyte signaling	Protein tyrosine phosphatase	Effects on function of T and B lymphocytes	Roque et al ¹⁹
Genome-wide association study and validation study	Boxer* GSD* Labrador Retriever Golden Retriever* Shiba Inu* Pit bull-type* West Highland White Terrier	11, 24 19, 38 64, 129 40, 66 23, 33 20, 17 18, 48	13 SNPs were associated with atopic dermatitis; 2 SNPs were associated with atopic dermatitis in all breeds.	Filaggrin in Golden Retrievers was implicated in atopic dermatitis	Resultant changes to protein that contributes to skin barrier	Wood et al ¹⁸
Candidate gene analysis	Boxer* GSD* Golden Retriever* Shiba Inu* Pit bull-type*	11, 24 19, 38 40, 66 23, 33 20, 17	SNP in TSLP receptor gene in all 8 breeds	TSLP receptor	Potential change in response to inflammation induced by the cytokine TSLP	Wood et al ¹⁹
Genome-wide association study	Labrador Retriever	151, 0	High serum concentrations of IgE against the storage mites <i>Acarus siro</i> and <i>Tyrophagus putrescentiae</i> associated to 2 different loci on chromosome CFA 5		High serum concentrations of allergen-specific IgE antibody	Owczarek-Lipska et al ¹⁷
Genome-wide association study	West Highland White Terrier	0, 52 Among these dogs, 31 had high concentrations of allergen-specific IgE; 21 dogs produced low concentrations of allergen-specific IgE	In dogs that developed high concentrations of allergen-specific IgE, there was an association of atopic dermatitis with a genomic sequence of 2.3 Mb on chromosome CFA 35		High serum concentration of allergen-specific IgE antibody	Roque et al ²⁰
Genome-wide association study	GSD (with low serum IgA concentration)	91, 88	Identification of 209-Kb region on chromosome CFA 27 that includes PKP2 gene	Plakophilin 2, which is involved in desmosomes and keratinocyte adherence	Resultant changes in protein that contributes to skin barrier	Tengvall et al ¹⁵
Genome-wide association study	GSD Labrador Retriever Golden Retriever West Highland White Terrier Boxer Bull Terrier Soft Coated Wheaten Terrier Others	91, 83 21, 14 10, 15 18, 15 22, 17 12, 7 2, 0 2, 41	Identification of cell-type specific SNPs in enhancer region for PKP2 gene		Resultant changes in expression of a protein that contributes to skin barrier	Tengvall et al ¹⁶

*The same dogs were used in 2 analyses.

GSD = German Shepherd Dog. Kb = Kilobase. Mb = Megabase. SNP = Single nucleotide polymorphism.