


# Canine Atopic Dermatitis: Prevalence, Impact, and Management Strategies

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**Abstract:** Atopic dermatitis (AD) is a common inflammatory and pruritic allergic skin disease in humans and dogs worldwide. The pathogenesis of AD is multifactorial, immunologically complex, and may involve genetic factors, epidermal barrier dysfunction, microbiome changes, immune dysregulation, and allergic sensitization. Across species, prevalence of AD is on the rise. At present, there is no cure for canine AD (CAD). The treatment for CAD is multifaceted and aimed at controlling the pruritus, associated inflammation, and infections, repairing the skin barrier function, and dietary management. This review presents data on prevalence, impact, and complex immunological interactions in AD with a focus on subsequent management of the disease in the canine population. A multimodal approach for management of CAD to address varying clinical signs and responses to therapies is discussed.

**Keywords:** immunopathology, topical therapies, systemic therapies, pruritus, immune therapies, alarmins

## Prevalence

Canine atopic dermatitis (CAD) is a multifactorial, pruritic disease, with genetic and environmental factors playing an important role in development and pathophysiology.<sup>1,2</sup> Skin barrier dysfunction and aberrant immune response are the characteristics of CAD.<sup>2,3</sup> The prevalence of CAD has been estimated at 3–15%.<sup>4</sup> However, as per the American College of Veterinary Dermatology (ACVD) task force on atopic dermatitis (AD), these percentages are not based on reliable epidemiological data, and the ACVD task force concluded that the actual incidence and prevalence of CAD in the canine population is not well known.<sup>5</sup>

Comparative studies of patients presented to veterinary facilities for skin diseases can be helpful to assess prevalence. In a study of dogs presented for skin problems at 52 veterinary practices in the US, prevalence of atopic or allergic dermatitis, and atopy, was 4.7% in 31,484 dogs examined.<sup>6</sup> In a study from the Small Animal Clinic at University of Montreal, 18.8% of the dogs presented for dermatological disorders of which 12.7% were atopic.<sup>7</sup> A recent retrospective study from a teaching hospital in Brazil reports an upward trend in diagnosis of CAD with 25.65% AD cases of all the dogs examined. Although the numbers from these studies provide insight into the cases presented, it is difficult to derive prevalence from these studies as populations at the teaching hospitals do not represent the general canine population.

Although many studies provide some insight on the prevalence of CAD, these data are influenced by geographical regions, survey methods, selection of populations, types of veterinary practices, and criteria used for diagnosis of CAD and other dermatoses.<sup>5</sup> The prevalence and risk of developing CAD is also influenced by environmental factors. Dogs living indoors have a higher frequency of developing CAD.<sup>8,9</sup> In a study of Golden and Labrador retrievers, environmental factors such as living in rural areas, or with other animals, and being walked in forest areas were associated with a decreased risk of CAD development, whereas, early adoption, and living in a shed in puppyhood were associated with a higher risk of CAD development.<sup>10</sup> Another study in Labrador and Golden retrievers reports factors such as dogs born in rural locations, living with other dogs, and those walked on woodlands, fields, and beaches reduced the risk of developing CAD.<sup>11</sup>

In general, the onset for clinical signs of CAD is between 4 months to 3 years of age.<sup>8,9</sup> However, the age of onset can vary between different breeds,<sup>12</sup> and thus cause a change in the prevalence reported per breed, especially if a breed is represented highly in a specific geographic area. Sex-related predispositions for CAD have not been reported, but studies have shown higher numbers in either sex. In a retrospective study from Brazil, where 25.65% of dogs presented to the teaching hospital were diagnosed with CAD, 62.4% were females.<sup>13</sup> However, studies have shown that male dogs, especially neutered males, are more likely to develop CAD than intact female dogs.<sup>11</sup> In a study from Australia, a higher risk in males from Pug and Bichon Frisch breeds was identified.<sup>14</sup> However, it should be noticed that most studies do not notice any sex predilection for development of CAD. In another study, a negative correlation between feeding a non-commercial homemade diet of the nursing dog and the development of CAD in her litter has also been reported.<sup>15</sup>

The prevalence of CAD also depends on the representation of specific breeds in geographical areas where studies are conducted. Multiple studies report that Golden Retrievers, Labrador Retrievers, West Highland Terriers, German Shepherds, and French Bulldogs are at an increased risk of developing CAD.<sup>3</sup> In a study from Australia, 11 dog breeds with significantly increased odds risk for CAD were identified worldwide, such as Boxer, Labrador Retriever, Pug, Bulldog, and West Highland Terrier, and classified as predisposed.<sup>14</sup> In a retrospective study from Brazil, CAD was most prevalent in mixed breed dogs, followed by Shih Tzu and Poodles.<sup>13</sup> Several factors influence the breed representations in CAD, including regional popularity of the breeds, genetic susceptibility, and geographical area.<sup>13</sup>

Despite all the studies, it should be noted that true prevalence and incidence of CAD is hard to determine due to the complex development, presentation, and management of the disease. Many CAD cases are managed by veterinarians without a specific diagnosis, such as mild presentations of CAD that are managed symptomatically or specific clinical presentations such as chronic otitis, which may not be identified as CAD by clinicians,<sup>5</sup> affecting incidence reporting. Furthermore, the influence of a variety of environmental risk factors in disease development affects the prevalence reported.<sup>1</sup> Considering all the factors that can affect diagnosis and presentation of CAD, there is a need for detailed epidemiological studies on the prevalence and incidence of CAD.

## Impact

The prevalence numbers discussed above indicate that CAD is a significant malady of the pet population. Veterinarians rely on clinical signs and behavior of the animal when assessing the effect of a disease on the wellbeing of pets. Diseases of pets can affect quality of life of the pets as well as that of their owners.<sup>16,17</sup> Since 2010, several questionnaires have been developed for skin diseases in small animals, and some of these also assess owner quality of life. Some questionnaires have been validated, and assessing quality of life in therapy studies is becoming more common.<sup>16</sup> In the study by Linek and Favrot,<sup>17</sup> almost half of the owners of dogs with CAD reported the disease affected their own quality of life, and a majority of owners felt the disease affected their pet's quality of life. Those effects included changes or interruptions in mood, family life, leisure activities, and sleep. Some owners were also concerned with expenses and the burden of treatment. The pet's quality of life was affected by changes in the dog's activities of playing, walking, and sleeping.<sup>17</sup>

There are studies that indicate pruritus and atopic dermatitis can affect canine behavior in negative ways. One study found increases in behaviors associated with fear, anxiety, aggression, and decreased trainability.<sup>18</sup> Another study did not find increases in fear and anxiety behaviors, while an increase in numerous unwanted or problem behaviors was identified, along with a decrease in trainability.<sup>11</sup> The authors postulated that behavioral changes could be related to stress associated with pruritus. Behavioral problems are potential reasons for euthanasia of companion animals. According to a study by Pegram et al, behavioral problems were one of the most common reasons for euthanasia of dogs in the United Kingdom.<sup>19</sup> However, the study by Linek et al did not show increased thoughts of euthanasia by the owners.<sup>17</sup>

CAD requires ongoing management that entails a long-term financial commitment from the pet owner, which may be a burden and could affect access to care in some instances. However, based on prevalence of the disease, the treatment and management of CAD is potentially a significant source of veterinary industry income. Information on the financial impact of CAD for patients, pet owners, and the veterinary industry, though, is limited. The inclusion of the use of quality-of-life data is helping to improve our understanding and treatment of CAD. There is a need for focused studies on the financial, pet behavioral, and human emotional impacts of CAD.

## Immunopathology

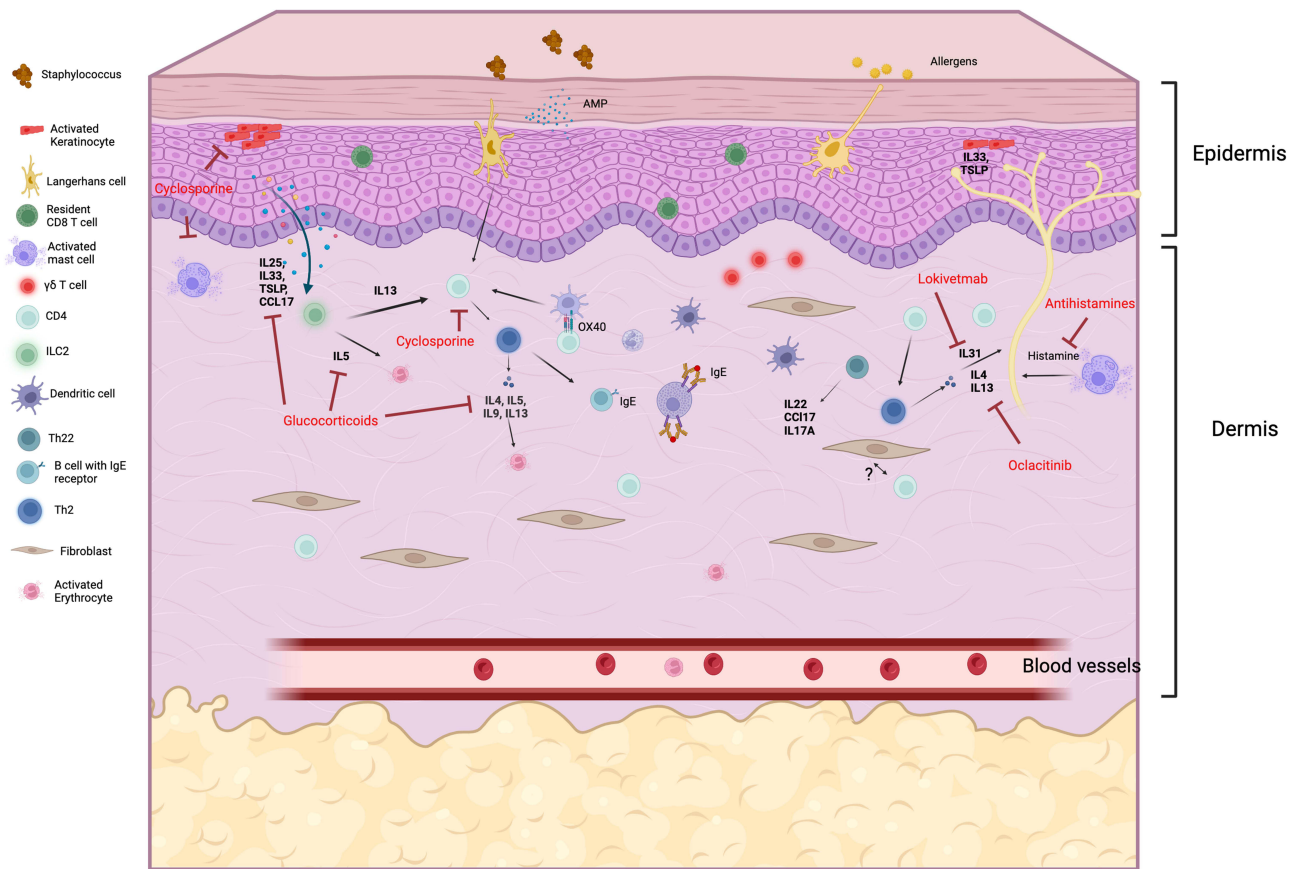
Initially, AD was understood simply as an IgE mediated allergic response or hypersensitivity I reaction, disrupting skin barrier function and activating Th2 responses. Different hypotheses were put forward, such as Outside-In with epidermal barrier dysfunction as primary cause leading to immune activation, or Inside-Out, where epidermal barrier dysfunction is secondary.<sup>20</sup> However, it has become evident that there are more nuanced and complex underpinnings of the disease, involving a variety of immune cell subsets and responses, types of barrier function disruption and neuroimmune feedback loops that contribute to pathophysiology.<sup>21–24</sup>

In healthy skin, a balance of skin barrier integrity, commensal skin microbiota, and cellular skin populations contribute to skin function and response to pathogens. Disruption of any of these factors leads to dysregulation of this balance with negative effects. Several strong candidate genes for development of AD in humans have been identified, such as mutations in filaggrin, an important epidermal protein,<sup>25</sup> or immune genes found in a cluster on human chromosome 5, such as IL4, and IL13 with over 30 loci implicated.<sup>26</sup> In dogs, recent genome-wide association studies (GWAS) on canine AD have also shown a strong connection with the filaggrin gene locus, and genes involved in immune responses and skin barrier function, with over 15 loci connected to CAD development.<sup>27</sup> As in humans, it is not clear how many mutations in these genes contribute to CAD. Certain dog breeds, such as German Shepherd dogs and Golden and Labrador retrievers, are overrepresented in prevalence of CAD.<sup>28,29</sup> However, while genetics play certainly a role, multiple factors including the environment and nutrition add to a complex trait such as AD, as evidenced by the fact that mutations are not found in all cases of AD, and even carriers of these mutations do not all develop AD.<sup>1,30</sup>

Epidermal barrier disruption promotes inflammation, either due to filaggrin mutation as a primary cause, or secondary, subsequent to inflammatory/immune signaling. Other causes of skin dysbiosis occur with the itch-scratch cycle caused by irritants or allergens. These disruptions favor colonization with opportunistic microbiota, negatively affecting the skin by creating a feedback loop between immune response and epidermal inflammation. *Staphylococcus spp.* are commonly found in atopic lesions, in both humans (*S. aureus*)<sup>31,32</sup> and dogs (*S. pseudintermedius*),<sup>33,34</sup> in conjunction with overall decreased microbial diversity.<sup>34</sup> Other microbiota found associated with AD skin are *Malassezia*,<sup>35,36</sup> or *Corynebacterium*.<sup>34</sup> All of these can aggravate already inflamed skin, and in several studies the use of antimicrobials and medicated shampoos has been found to be beneficial in combination with other treatments for AD,<sup>37,38</sup> however, there is concern about increasing resistance of bacteria with the continued use of antibiotics.<sup>39</sup> As with epidermal barrier dysfunction, changes in microbiota community diversity and prevalence might be primary or secondary to AD development.

In non-lesional skin and early acute stage of AD, tissue damage leads to the release of a class of proteins by keratinocytes, such as IL25, IL33, or thymic stromal lymphopoietin (TSLP), which are also called alarmins,<sup>40–42</sup> and chemokines CCL17 and CCL22<sup>43</sup> (Figure 1). Alarmins are strong activators of Innate Lymphocyte Cell type 2 (ILC2) which release IL5 and IL13, both cytokines involved in TH2 signaling.<sup>42,44</sup> ILC2 has been found in acute AD lesions of humans and mice,<sup>42,45</sup> but have not been investigated in the skin of dogs. A study on peripheral blood in atopic dogs did not show elevated levels of these cells, which is in agreement with studies on ILCs in human patients.<sup>46</sup> The alarmin TSLP has been shown to activate dermal dendritic cells to express OX40 and consequently activate naïve CD4 T cells, further amplifying a Th2 response.<sup>47–49</sup> Expression of TSLP was significantly increased in lesional and nonlesional skin of dogs with CAD.<sup>50</sup> Another aspect of alarmin release from keratinocytes, particularly TSLP and IL33, is the subsequent initiation of itch sensations. Scratching leads to more epidermal damage, followed by more release of alarmins, release of histamines from a variety of cells including mast cells, and Th2 mediated activation of IL31, which acts on sensory neurons to induce an itch sensation.<sup>51,52</sup> The itch-scratch cycle reinforces itself and can eventually lead to thickening of the epidermis and chronic inflammation.

Chemokines CCL17 and CCL22 also induce Th2 responses, and combined, these inflammatory events lead to a self-amplifying release of IL4, IL5, IL13, and IL31, increased infiltration of CD4 and CD8 T cells, activation of B cells and IgE class switching, activation of mast cells, and recruitment of eosinophils.<sup>44,53,54</sup> The key intracellular pathway involved in inflammatory and particularly Th2 signaling is Janus activated kinase/signal transducer and activator of transcription (JAK/STAT) mediated,<sup>55</sup> where binding of cytokines to their cellular receptors activates JAK, leading to phosphorylation of STAT inducing gene transcription of inflammatory signaling molecules. Due to its importance in Th2 signaling, this pathway has become a major focus for drug development to combat pruritus and inflammation in AD.



**Figure 1** Immunological pathways and relevant therapeutic interventions in the canine atopic skin. Several cell types are involved in inflammation in the skin, including keratinocytes, fibroblasts, dendritic cells, mast cells, several subpopulation of T lymphocytes and B lymphocytes. Different cytokines and other inflammatory mediators are released by various cells and can be targeted by topical and systemic therapeutics. Created with Biorender.com.

**Abbreviations:** ILC, Innate lymphoid cells; IL, Interleukin; AMP, antimicrobial peptides; TSLP, thymic stromal lymphopoietin; IgE, immunoglobulin E.

Aside from Th2, several studies have looked at Th1, Th9, Th17 and Th22 activation both in humans and dogs.<sup>53,56–58</sup> The involvement of additional cell types and cytokines is reflective of an increasingly complex and widening adaptive immune response, transitioning to chronic disease. Th22 is associated with expression of IL22, which is present in the onset of acute lesions, progressively increasing in chronic disease.<sup>56</sup> On the other hand, Th1 and Th17 tend to be more variable in chronic stages of AD, but are also associated with bacterial colonization, as both of these pathways are typically considered classic inflammatory pathogen responses.<sup>59</sup> Different endotypes of atopic dermatitis in humans have been shown to reflect differences in the activation of these Th responses.<sup>44,60</sup> As an added complication, in humans difference in Th1 vs Th22 or Th17 involvement has been associated with ethnicity, with European vs Asian subtypes, but recent transcriptomic studies reveal a rather heterogeneous pathogenesis involving Th17, Th22, and Th1 types.<sup>44,59–61</sup> Dog breed-specific Th subtypes have so far not been identified.

Recent advances in single-cell transcriptomics are increasingly delineating these complex responses on a cellular level both in humans and dogs.<sup>22,62,63</sup> Not only do these studies show the cellular subpopulations and detailed activated genes and pathways involved but also identify different cells previously not well investigated in the context of AD. For example, fibroblasts were identified in these single-cell sequencing studies as having a role in immunomodulation, opening up new avenues of investigation for therapeutics. In the canine study, gamma delta T cells were additionally identified as highly increased in the atopic skin of dogs, and several inflammatory markers previously not detected discovered.<sup>63</sup>

Considering the variability of responses, but common themes such as Th2 responses, neuroinflammation and itch, the treatment of CAD has focused on the pathways involved in these areas as detailed in the following management practices.

## Management of CAD

CAD requires a multimodal approach for management. Each dog has varying degrees of clinical signs and responses to therapies; thus, it is best to tailor the management plan for each individual patient. It is also important to emphasize that secondary infection and other factors need to be addressed for these management strategies to be effective. Clinicians should always treat for secondary bacteria and yeast pyoderma or pododermatitis prior to reaching for symptomatic care, especially when there is a sudden increase in the pruritus score or if a patient's pruritus is localized. Of equal importance, it is pertinent to investigate other causes of pruritus with diet trials and parasite control. If there is a limited response to these management therapies, clinicians should reconsider their diagnosis. Lastly, to ensure successful long-term management, client education is most essential. Chronicity and incurable aspects of CAD in addition to expectations ought to be addressed. Frustration and ongoing expenses are common concerns, and owners should be counseled accordingly.

## Immunotherapy

Allergen-specific immunotherapy (ASIT) has been at the forefront of managing AD in both humans and veterinary patients since 1911.<sup>64–66</sup> The first report of successfully treating an allergic dog with ASIT was published in 1941.<sup>67</sup> It is the most effective and proactive way to manage CAD. ASIT is generally safe, helps reduce clinical signs, and decreases the overall need for medication.<sup>68</sup> ASIT refers to a mix of allergens given in progressively increasing doses and typically consists of an induction phase followed by maintenance. Traditionally, these doses are given as subcutaneous injections. Frequencies and amounts should be customized to each individual depending on the individual's clinical responses and adverse events. The average observable clinical response occurs between six and eight months but because response rates are variable, subcutaneous ASIT should be continued for at least 1 year to properly evaluate efficacy.<sup>64,68,69</sup> For some patients, especially seasonal cases, 2–3 years of follow-up are needed to make a suitable assessment. According to a retrospective study of 664 client owned dogs, more than 50% of clinical signs improved in 59.9% of atopic dogs with ASIT. Beneficial effects are notably higher if dogs are examined regularly and consistently, and if no systemic long-term corticosteroids are given in the first 9 months of therapy.<sup>70</sup> Nevertheless, owner compliance is the main factor as the cause for reduced efficacy of ASIT. In another retrospective study of 145 CAD patients managed with ASIT, the duration of treatment was strongly linked with efficacy.<sup>71</sup> Dogs treated for less than 1 year only showed an efficacy rate of 22% compared to dogs treated for more than 1 year (65%). In addition, concomitant medications in dogs treated for more than 1 year were reduced by 87%.<sup>71</sup>

Some clinicians, including the authors of this paper, have found RUSH ("sped-up") immunotherapy to be an effective protocol because RUSH immunotherapy can decrease the time necessary to achieve maintenance doses as well as reducing questionable side effects monitored by owners. In RUSH protocols, doses are administered at 15–60 minute intervals over 1–3 days, until maintenance is achieved.<sup>72</sup>

Sublingual immunotherapy (SLIT) is a form of immunotherapy where allergens are given orally instead of by traditional subcutaneous injection. For humans, it has been an efficacious treatment and received United States regulatory approval in 2014.<sup>73</sup> In people, the major use is for allergic rhinoconjunctivitis or asthma but has also been used for AD.<sup>74,75</sup> Protocols usually include hooking the plastic dispensing nozzle over the lower arcade of teeth or the commissure, with the goal that the solution be dispensed sublingually.<sup>74</sup> Protocols generally consist of an induction period ranging from lower to higher concentrations but can vary. Most protocols consist of one to two pumps twice daily. Patients should avoid eating or drinking for 10 minutes before and after administration for best absorption.

Intra-lymphatic immunotherapy (ILIT) is a relatively new form of ASIT.<sup>72,76</sup> In dogs, protocols include administration with ultrasound guidance into a lymph node, usually the popliteal, as it is the easiest lymph node to access. Induction phases can vary but one published protocol consists of one injection every 4 weeks for four treatments, followed by the maintenance phase of subcutaneous ASIT injections thereafter.<sup>76</sup> In a prospective comparison study comparing three different protocols (subcutaneous ASIT, ILIT and SLIT), ILIT outperformed both groups in returning to normal and improvement. In another study, no significant differences between RUSH immunotherapy and ILIT induction protocol were noted.<sup>72</sup> ILIT has been found to be safe and identical in efficacy to traditional subcutaneous ASIT.<sup>75</sup>

Currently, there is no standardization for immunotherapy protocols no matter the methodology. Protocols can be used as a starting point, but the clinician should make adjustments based on each individual patient's response. Presently, it is

essential to highlight that CAD is a diagnosis via exclusion and that neither ASIT nor IgE serologies can be used to diagnose CAD. Yet these diagnostics are helpful in identifying hypersensitivity to environmental allergies in CAD patients after a diagnosis has been made.

## Drugs

Antihistamines make a minor impact on the overall management of CAD, but they continue to be one of the most frequently used medications to manage CAD.<sup>77</sup> Type I oral antihistamines include hydroxyzine, diphenhydramine, chlorpheniramine, clemastine, and dimetindene. Their principal mechanism of action was considered to interfere with histamine-mediated pruritus by blocking the histamine H<sub>1</sub> receptor.<sup>78,79</sup> Histamine is an inflammatory mediator released from several cells, such as mast cells and basophils, leading to further degranulation of mast cells and inflammatory cell migration and is thought to be involved in the excitation of unmyelinated C-fibers via increase in calcium in neurons, leading to itch.<sup>80,81</sup> First-generation antihistamines block histaminic and muscarinic receptors and are able to pass the blood–brain barrier.<sup>82</sup> Second-generation antihistamines predominantly block histaminic receptors and are less likely to pass blood–brain barrier.<sup>82</sup> First-generation antihistamine studies tend to have conflicting results, but it can be agreed that results are generally trivial or ineffective. A randomized control trial reported that two first generation oral antihistamines, consisting of a hydroxyzine/chlorpheniramine combination (Histacalmine<sup>®</sup>, Virbac, Carros, France) and dimetindene (Fenistil<sup>®</sup>, Novartis, Basel Switzerland) barely improved dermatological lesions and pruritus in dogs with CAD.<sup>83</sup> In contrast, the development of skin lesions in an experimental model of acute CAD in house dust mite-sensitized dog was not prevented by the administration of hydroxyzine.<sup>78</sup> In another study, it was demonstrated that cetirizine, a second-generation antihistamine, had no effect on pruritus after 14 days of administration in chronic CAD patients.<sup>79</sup> Loratadine, cetirizine, and fexofenadine are commonly prescribed second-generation antihistamines.<sup>84</sup> For optimal benefit, it is recommended that type I antihistamines be given either prior to a flare, or given to dogs with mild forms of CAD.<sup>68</sup> Certain antihistamines (hydroxyzine, cetirizine, and cyproheptadine) may also block serotonin receptors.<sup>69</sup> Some antihistamines modify behavior, notably, tricyclic antidepressants that include amitriptyline and doxepin. Adverse effects are often mild, largely being pruritus, but dry mouth, panting, sedation, drowsiness, hypersalivation, ataxia, trembling, hyperesthesia, and excitation have all been reported.<sup>69</sup> Second-generation antihistamines should theoretically provide fewer side effects because they do not pass the blood–brain barrier, but this is not guaranteed.<sup>84</sup> Despite all these negative data, in a study performed by Dell and collaborators, owners believe antihistamines to be an effective part of multimodal therapy for CAD.<sup>77</sup> Benefits are only seen in a minority of dogs and benefits usually occur in the first 7–14 days of treatment.<sup>80</sup> Antihistamines are better suited as an additive or used synergistically with other medications.<sup>80</sup> Their lack of efficacy is probably linked to the fact that histamine is not the only molecule causing pruritis, as detailed in the immunopathology section.

Glucocorticoids have powerful immunologic and anti-inflammatory activities. They exhibit many inhibitory effects directly acting on target genes, subsequently affecting the production of inflammatory mediators as well as induction of anti-inflammatory cytokines and thereby modulating cell-mediated and humoral immunity.<sup>69</sup> Glucocorticoids are effective and work quickly, but without proper management, undesirable adverse effects can occur. Typically, oral glucocorticoids are used for managing CAD. Oral prednisolone, prednisone, and methylprednisolone are given at 0.5–1 mg/kg per day.<sup>69</sup> Adverse effects are generally proportional to steroid potency, dosage, and administration duration. Long-term control of CAD is best accomplished with alternate days of glucocorticoid therapies, at once every 48 hour or 72-hour dosing, to diminish side effects. Side effects include varying degrees of hypercortisolism-polydipsia, polyuria, polyphagia, weight gain, calcinosis cutis, dermal atrophy, pyoderma, panting, urinary tract infections, distended abdomen, depression, and diarrhea.<sup>69</sup>

Cyclosporine is an immunosuppressive drug that was originally developed to prevent organ transplant rejection.<sup>69</sup> It is desired for its immunosuppressive benefits compared to its low cytotoxicity effects and does not interfere with the results of intradermal skin tests.<sup>69</sup> Cyclosporine inhibits intracellular calcineurin, which is a serine/threonine protein phosphatase involved in activation of T cells. The enzyme dephosphorylates nuclear factor of the transcription factor called “nuclear factor of activated T cell cytoplasmic” (NFATc). Transcription factors function by translocation to the nucleus with subsequent binding to the promoter of a gene, inducing its transcription, which in case of NFATc includes interleukin-2 (IL-2), an

important cytokine for T cell activation and proliferation. By blocking calcineurin, dephosphorylation and subsequent translocation of NFATc is blocked, decreasing IL-2 release and therefore T cell activation. Cyclosporine has been extensively used to treat CAD and many other diseases; its advantageous effects extend beyond IL-2 suppression as cyclosporine affects canine keratinocytes, potentially cutaneous dendritic cells, inhibits mast cell degranulation, and innate immunity.<sup>69,85</sup> Different cyclosporine formulations are available: veterinary, human brand-named, and generic formulations. Microemulsified formulations are preferred, as the microemulsion concentration is absorbed quickly and effectively through the gastrointestinal tract of dogs. The problem with cyclosporine is variability in its bioavailability, between dogs and even in the same dog. Presence of food in the gastrointestinal tract can play a role in making bioavailability even more variable, especially when food is high in fat, so it was recommended to administer ultramicronized cyclosporine 2 hours before or after feeding.<sup>85,86</sup> Conversely, a study demonstrated that food did not have any impact on the efficacy of ultramicronized cyclosporine clinically.<sup>87</sup> At CAD specific dosing (5mg/kg PO per day), common side effects include vomiting, diarrhea, and anorexia. Less frequently observed side effects include hypertrichosis, gingival hyperplasia, papillomatosis, and psoriasiform lichenoid dermatosis.<sup>69,86</sup> There is often delayed gratification as it may take 4 weeks of therapy to see optimal clinical responses. The authors recommend prescribing name-brand veterinary formulations of cyclosporine at the optimal dosing daily until remission is achieved before tapering to the lowest effective dose or using modified versions. In most cases, this includes daily administration for 1 month before tapering. Cyclosporine is metabolized in the liver and intestines, by the cytochrome P450 isoenzymes, specifically CYP3A4.<sup>85</sup> Drugs inhibiting or inducing cytochrome P-450 may affect cyclosporine metabolism. CYP3A4 inducers, for example rifampin or carbamazepine, may decrease cyclosporine levels by increasing their clearance. On the other hand, P-450 inhibitors, most notably several antifungal drugs (ketoconazole, itraconazole, and fluconazole), decrease cyclosporine clearance and increase cyclosporine concentration.<sup>69</sup> Some clinicians take advantage of this by combining cyclosporine with ketoconazole. When used in combination, cyclosporine can be reduced to 2.5 mg/kg PO per day, but note that this is a calculated hypothesis and true dosing would vary individually. While this is a method to decrease cyclosporine, the authors see a higher incidence of adverse effects and each patient's bioavailability is variable so the reduction serves only as a guide. Some clinicians use trough and peak cyclosporine levels to provide guidance.

Oclacitinib (Apoquel<sup>®</sup>, Zoetis, Parsippany-Troy Hill, NJ) is an immune-modulating drug that inhibits the JAK/STAT signaling pathway. As previously mentioned, this pathway plays a major role in Th2 mediated inflammatory responses. It has been approved for treating pruritus related to allergic dermatitis, including CAD.<sup>88</sup> Oclacitinib has been popular among clinicians for its high degree of efficacy, rapid onset, and like cyclosporine, no interference with intradermal skin testing, and low degree of adverse effects. The labeled prescribed dosing is 0.4–0.6 mg/kg PO every 12 hours for up to the 14 days<sup>89</sup> and then once daily for maintenance according to manufacturer's instructions. However, the authors find that most cases do not require this induction dosing. Oclacitinib allows comparable reduction in pruritus and clinical signs, compared to prednisolone, and outperforms cyclosporine in pruritus resolution and speed of action.<sup>90–92</sup> Side effects, mainly gastrointestinal signs, are rare. Skin infections are also noted as side effects,<sup>88</sup> but dogs with CAD tend to develop recurrent skin infections without medications. At the label dose, changes in hematological and serum chemical parameters have been described, but are minimal, including slight leukopenia, mild hypercholesterolemia, and minor increases in alkaline phosphatase (ALP) activity levels.<sup>88</sup> Apoquel<sup>®</sup> should not be administered in dogs less than 12 months of age, nor in dogs with serious infections, such as pneumonia. Apoquel may exacerbate neoplastic conditions or increase susceptibility to infection, notably demodicosis. There is now a chewable formulation available for dogs.<sup>93</sup>

Lokivetmab (Cytopoint<sup>®</sup>, Zoetis, Parsippany-Troy Hill, NJ) is indicated for the treatment of clinical ailments of CAD. It is a caninized anti-interleukin (IL)-31 monoclonal antibody that was designed to neutralize IL-31,<sup>94</sup> which is a cytokine acting on sensory neurons in the skin causing neuroinflammation and itch.<sup>52</sup> It is commercially available as a subcutaneous injection in 1 ml vials containing 10, 20, 30, or 40 mg of lokivetmab. The recommended minimum dose<sup>95</sup> is 1 mg/kg bodyweight once a month. Contraindications include not using in cases of hypersensitivity and dogs that weigh less than 3 kg, according to manufacturer's instructions. In a study of 274 CAD dogs, lokivetmab administered at about once monthly dosing of 1 mg/kg, provided pruritic relief within a day, lasting duration, and all with a good safety profile.<sup>96</sup> Another study confirmed the same findings.<sup>97</sup> A recent 2021 study found that a single subcutaneous injection of 2 mg/kg suppressed pruritus within 3 hours for forty-two days; however, this study was performed with purpose bred Beagles.<sup>98</sup> In a study performed by Marsella and collaborators comparing prednisone,

ocloctinib, cyclosporine, and lokivetmab for treatment of CAD in which dogs were challenged twice weekly with allergens, lokivetmab could be applicable in preventing flares and improving Transepidermal Water Loss (TEWL).<sup>99</sup>

Pentoxifylline is a methylxanthine derivative that produces diverse physiological changes at the cellular level, such as white blood cell kinetics (responsiveness and activity), and platelet deformability and aggregation. It is used for a variety of inflammatory diseases. In a study performed by Singh and collaborators, pentoxifylline only provided low-quality evidence for the management of CAD.<sup>100</sup> Pentoxifylline is available in a 400 mg coated tablet and dosing recommendations range between 20 and 30 mg/kg orally every 8–12 hours. Caution regarding the bioavailability of generic drugs ranging from 25% to 75%. Favorable response is not seen until 1–3 months of taking this drug. In general, serious side effects are not reported. Vomiting and diarrhea are seen infrequently. Dizziness and headaches have been reported in humans.<sup>101</sup>

## Topical Active Ingredients

### Antipruritics

Topical steroids are the mainstay of CAD topical treatments and are popular for their ability to quickly reduce inflammation and pruritus, ability to treat focal areas, and rarely produce undesired side effects in the short term. Topical glucocorticoids interfere with the inflammatory cascade and pruritogenic pathway by impeding the arachidonic acid pathway, some inflammatory cytokines, and growth factors and decreasing some adhesion molecules expression.<sup>102</sup> Glucocorticoids come in varying degrees of potency and different formulations and should be considered when formulating a treatment plan. In North America, topical glucocorticoids are divided into seven classes based on their ability to cause blanching (vasoconstriction).<sup>102</sup> Mild glucocorticoids (classes 6 and 7) are preferred when lesions are mildly inflamed, large areas to be treated, or thin skin at site of application (glabrous regions). These classes are preferred for long-term use. Ointments have an occlusive nature and improve glucocorticoid absorption but may also macerate in occluded areas (skin folds, high hair density, and interdigital spaces).<sup>102</sup> Creams are mixes of water suspended in oil. They are usually moisturizing and cosmetically acceptable but are generally less potent than ointments. Whatever delivery vehicle is chosen, it is not generally recommended that a topical steroid be applied more than twice a day.<sup>102</sup> Hydrocortisone was the first to be used and is most commonly found in commercial formulations.<sup>69</sup> Previous studies have noted adrenal suppression in formulations containing betamethasone, triamcinolone, and fluocinonide.<sup>69,103</sup> When choosing a steroid, it is best to choose a less potent steroid such as hydrocortisone 1% or a soft steroid to avoid overuse causing undesirable side effects. Soft steroids include a new generation of diester topical glucocorticoids: hydrocortisone aceponate, mometasone furoate, and prednicarbate. These are metabolized at skin level into inactive ingredients, thereby dramatically reducing unwanted systemic effects.<sup>104</sup> Triamcinolone acetonide and betamethasone are typically found in veterinary prescribed formulations of topical glucocorticoids. These are moderate-to-high potent glucocorticoids, and side effects are common with misuse. In the United States, triamcinolone acetonide is commonly found as a cream or ointment and combined with neomycin and nystatin and betamethasone is found as a topical spray combined with gentamicin. Triamcinolone acetonide spray (Genesis<sup>®</sup>; Virbac, Carros, France) has been shown to be very efficacious in the treatment of CAD if applied for 4 weeks then tapered in the absence of clinical adverse effects. Of note, there is a commonly used product in the United States that contains neomycin sulfate, isoflupredone acetate, and tetracaine hydrochloride (Neo-predel<sup>®</sup>; Zoetis, Parsippany-Troy Hills, NJ). It is popular for desired effects of drying out moist lesions, but owners should be counseled as even mild overuse can quickly lead to undesired adverse effects. For all glucocorticoids, caution should be taken when applying on glabrous regions of the body, notably the abdomen, because undesired effects of dermal atrophy, scaling, comedones, or even calcinosis cutis, can occur quickly and most commonly in those locations.<sup>69</sup>

Pramoxine hydrochloride is a topical anesthetic and is used as an antipruritic. It is an effective surface anesthetic and is well tolerated by skin and mucous membranes with extremely low rates of toxicity.<sup>69</sup> Pramoxine exerts its anesthetic and anti-pruritic effect by preventing excitation of slow C fibers that signal itch and pain. This is achieved by reversibly binding voltage-gated sodium channels preventing membrane depolarization, and subsequently inhibiting the generation of action potentials in these peripheral neurons.<sup>69</sup> Rarely, contact reactions are seen. One crossover open clinical trial evaluated two formulations of pramoxine cream rinse and concluded that after 4 weeks, there was at least 50% reduction in pruritus from 41% of the owners and antipruritic effects lasted 48 hour.<sup>104,105</sup> Unfortunately, with frequent and repeated use, duration of effect and efficacy wanes.<sup>106</sup> In veterinary medicine, it is usually found in the form of a shampoo, rinse, and spray and often

in combination with ceramides or hydrocortisone, and combination formulations serve dual moisturizing and antipruritic effects.

Tacrolimus has been explored for the treatment of localized lesions of atopic dogs.<sup>104</sup> Three studies have concluded that although expensive, tacrolimus is promising for managing localized CAD lesions with nominal side effects. Most dogs were able to reduce at least 50% of clinical signs from baseline after 4- to 12-week treatments.<sup>107</sup> Adverse effects of mild irritation were noted in a minority of cases: 0.1% ointment formulation is recommended due to 0.3% tacrolimus causing a fourfold increase in serum tacrolimus concentrations.<sup>108</sup>

### Emollients and Moisturizers

Since CAD patients have skin barrier defects, replenishing the oils can be beneficial in controlling clinical signs. Emollients are vehicles that soften, lubricate, or soothe the skin. Moisturizers aide by reducing TEWL via hygroscopic molecules or blocking agents. There are many options:

Fatty acids are important in hydration and serving as a barrier in controlling TEWL. Commercial products are direct topical applications of fatty acids to the skin. Dersoscent Essential 6<sup>®</sup> Spot-on (Nextmune, Phoenix, AZ) contains a combination of fatty acids and emollients that restore hydrolipidic film on the skin, maintain hydration, and maintain epidermal barrier function. In addition, inflammation is controlled with antioxidant and anti-free radicals. There have been several studies proving the efficacy of these essential fatty acids in reducing TEWL and pruritus scores with no side effects.<sup>109,110</sup> An induction dosing of one pipette every week for 2 months followed by maintenance dosing of one pipette every 2 weeks for as long as necessary according to manufacturer's instructions. No massage is required, and it is recommended not to bathe 2 days before and after application. The amount of product per pipette depends on the size of the pet: up to 10 kg, 10–20 kg, and 20–40 kg. The fragrance is a fresh herbal scent. Another product, Atopivet<sup>®</sup> Spot-on (Dechra, Cheshire, CT) contains Biosfeen<sup>®</sup>, a sphingomyelin-rich sphingolipid, and Dermial<sup>®</sup>, a glycosaminoglycan, specifically hyaluronic acid. The fragrance is a lavender scent. It comes in 2mL pipettes and can be applied to affected areas or between the shoulder blades and down the back twice weekly for at least 5–8 weeks before modifying the application as needed. It also comes in a mousse and skin care collar. The collar only contains Biosfeen<sup>®</sup> and can help the skin barrier for up to 2 months.

Coconut oil has been a very popular remedy with self-directed owners in recent years. Virgin coconut oil is preferred since it is colorless, odorless, and cosmetically elegant, and has antibacterial activity. For coconut oil to be clinically effective, it must be applied twice daily for at least 4 weeks.<sup>111</sup> This was adapted from human literature, and for dogs, the challenge is reaching skin level with hair being a barrier.

Mineral oil/liquid paraffin (highly refined mineral oil) baths also aid in reducing TEWL. In this protocol, the first step is to bathe the patient with a shampoo. The chosen shampoo should be decided based on the patient's presentation. If a patient tends to present with secondary infections, then an antiseptic shampoo should be recommended. If the patient tends to present with scale, then the clinician can prescribe a keratolytic or keratoplastic shampoo. It may be prudent to warn the client that for the first couple of baths, alopecia may be expected from dislodging affected hairs. The second step is to formulate a 50:50 mixture of water and mineral oil. This step replaces the lipid matrix of the stratum corneum. Soak the patient for 1 hour, to allow the oils to penetrate. In the final step, the patient should be washed with dishwashing soap to break down excess oils. Another option is to use large puppy pads to soak up the excess oil. The authors prefer the brands Alpha Keri and Patterson Medical unscented paraffin oil.

Wet wrapping is a protocol adapted from human literature to control atopic eczema in children.<sup>112,113</sup> This protocol is effective for rehydrating and calming the skin, as well as helping topical medications work better. Fill the bathtub with lukewarm water, then add liquid paraffin. Immerse the pet minus the head for 5 min. Remove the pet and pat (not rub) dry. Cover the skin with a thick moisturizer or emollient. For severely pruritic pets, mometasone furoate 0.1% ointment is advised on pruritic areas as this is a soft steroid and theoretically will not be absorbed systemically. Next, place fitted clothes and/or socks in hot water and wring them out, then dress the patient. Apply a second layer of fitted clothes and/or socks, leave on for 40 minutes or until the dressing is dry. Perform once daily until the patient is less pruritic or two to three times a week if steroids are used. Clients will commonly need to make adjustments to the fitted clothes and socks for desired effects. Socks should extend to above the second joint to avoid slippage. Human studies have repeatedly demonstrated the efficacy of wet wrapping with topical corticosteroids, resulting in an improved quality of life and

avoiding systemic therapy. It is prudent to warn caretakers of this laborious and time-consuming task, but relief is almost immediate and can avoid systemic therapy.<sup>112,114,115</sup> The authors often reach for this therapy for patients who have had adverse effects to systemic CAD medication.

## Nutrition

The most important essential fatty acids (EFAs) in cutaneous homeostasis in dogs are linoleic acid (18:2N-6) and alpha-linoleic acid (18:3N-3). The proposed mechanism of how EFAs function in controlling pruritus includes inhibition of arachidonic acid metabolism in favor of dihomo-gamma-linolenic acid (DGLA). The final product of DGLA metabolism is prostaglandin E<sub>1</sub>, which is thought to have anti-inflammatory effects.<sup>69</sup> There are unsatisfactory evidence-based studies supporting the use of EFAs; ultimately, results depend on the source, amount, and duration of supplementation.<sup>116,117</sup> It has been proposed that an adequate therapeutic trial might necessitate 3–4 months of use<sup>69</sup> and that EFAs may have a steroid sparing effect.<sup>117</sup> Side effects are rarely reported but can consist of vomiting, diarrhea, weight gain, unpleasant odor, or “fish breath”.

Probiotics have recently gained attention. Many studies have shown a significant and synergistic connection between the gastrointestinal and dermatological systems, and scientific evidence link gastrointestinal homeostasis to cutaneous manifestations.<sup>118–120</sup> Knowledge as to the exact mechanisms of the link are still being investigated, but it is thought that interactions between the microbiome and the intestinal immune system results in modulation of immunity with effects on many other systems beyond the gut. Many skin diseases, including atopic dermatitis, seem to be related to gut dysbiosis. Modulation of canine intestinal microbiota is getting more attention as a taking part of multimodal CAD management. The exact mechanism of action of probiotics still needs further investigation, but like immunotherapy, it appears that the immune response might shift towards a Th1 mediated response, instead of Th2, which is detrimental in AD.<sup>121</sup> In a recent study, probiotics played a role in CAD management as a complimentary or steroid sparing therapy.<sup>122</sup>

Zinc plays a role in skin health and proper immune function and in the management of some skin diseases.<sup>123</sup> In a 24-week, randomized, double-blinded controlled crossover study with 27 dogs, atopic dogs receiving glucocorticoids and zinc methionine supplementation may benefit in both clinical response and pruritus levels.<sup>124</sup>

Vitamin D has been a hot topic as part of multimodal therapy for many diseases including atopic dermatitis. Vitamin D is involved with skin barrier function and immune response, including the production of antimicrobial peptides. It has been associated with severe allergic diseases in humans, but the role of vitamin D in CAD is still in development. It has been shown that CAD has been associated with low vitamin D and that supplementation CADESI and pruritus has been associated with increased serum levels.<sup>125</sup> There is also evidence that canine mast cell tumor growth is inhibited by vitamin D because in one study, Labrador Retriever dogs with low vitamin D levels had an increased chance of developing mast- cell tumors.<sup>126</sup> Overall, at this time, there is insufficient evidence to determine vitamin D’s role in the development or pathogenesis of CAD.

Palmitoylethanolamide PEA, a type of cannabinoid receptor agonist, has been used in CAD management as part of multimodal therapy. PEA-Cannabinoid receptors (CB1, CB2) are expressed on endothelial cells, mast cells, and canine keratinocytes. Immunohistochemical staining indicated increased cannabinoid receptors in the dermis of atopic dogs, compared to their healthy counterparts. Treatment with cannabinoid receptor agonists, such as Palmitoylethanolamide or PEA, has been shown to decrease mast cell degranulation, histamine-related pruritus, and vasodilation. It has also been demonstrated that skin levels of endogenous PEA are higher in atopic dogs.<sup>127</sup>

In recent years, commercial diets aimed specifically for canine atopic dermatitis are available. Examples include Hill’s Derm Complete<sup>®</sup> and Royal Canin’s Skintopic<sup>®</sup>. Hill’s Derm Complete is an egg-based diet that has the HistaGuard Complex, which contains bioactives and phytonutrients that help reduce allergic response. Phytonutrients help decrease inflammatory cytokines, mast cell degranulation, and interfere with dendritic function and maturation. Royal Canin’s Skintopic features a patented Dermauxillium Complex, a unique blend of nutrients and antioxidants to aid in supporting skin and coat health. In a double-blinded placebo-controlled study, pVAS and CADESI-04 scores were improved by at least 30–50%, and drug-sparing effect could be observed within 3–6 months after starting the new diet.<sup>128</sup>

## Environmental Control

Allergen avoidance should be considered whenever possible, although this is frequently difficult to accomplish. Bathing can help minimize cutaneous exposure as well as wiping the patient after outside exposure to minimize allergen exposure contact. Patients with pollen and plant allergies should not be outside when grass is mowed or on windy days. Ideally, inciting plants should be removed from the patient's environment whenever possible. For house dust and molds, high efficiency particulate air (HEPA) filters air purifiers and frequent housekeeping should be implemented, such as increased frequency of vacuuming and changing bedding. Dogs should be removed from the property during these activities to limit exposure.

## Conclusion

Considering the complexity of CAD pathophysiology, treatment needs to be on an individual basis, taking into consideration all factors, such as genetics, nutrition, and environment. However, further research is needed, as no treatment is 100% successful, and in some cases even with a combination of treatments, relief is not achieved. None of the current drugs are curative and will require lifelong use in some cases, putting a financial burden on patients or clients. There are many more therapeutics in the pipeline specifically in human medicine, which can translate to new therapies for dogs, albeit at a high cost, as many newer treatments are biologicals. Finding therapies that can successfully address the root cause and disrupt the cycle of insult and inflammation will require additional research and probably a wider approach looking at cells and pathways previously not investigated. With increased advances in technology, further elucidating the complex interactions of cells in the skin, this goal is achievable.

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