



## Comment and Controversy

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# Atopic dermatitis in the domestic dog



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**Abstract** Dogs may develop a syndrome of spontaneous, inflammatory, pruritic dermatitis that shares many features with human atopic dermatitis, including a young age of onset, characteristic lesion distribution, immunoglobulin E sensitization to common environmental allergen sources, and evidence of epidermal barrier dysfunction. There are also several important differences between canine and human atopic dermatitis. Although dogs may suffer from multiple-organ hypersensitivity syndromes, there is no evidence that this species experiences the progressive evolution from cutaneous to respiratory allergy characteristic of the human atopic march. Despite the presence of epidermal barrier derangement, there is no significant association between canine atopic dermatitis and mutations in filaggrin. Finally, treatment of canine disease relies much less heavily on topical therapy than does its human counterpart, while allergy testing and allergen-specific immunotherapy provide an often essential component of effective clinical management of affected dogs.

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## Introduction

The domestic dog is one of the few nonhuman species to develop spontaneous allergic skin disease. In 1941, Frederick William Wittich (1885–1965), an allergist from Minneapolis, described a dog that developed seasonal “atopic” rhinitis and pruritic dermatitis.<sup>1</sup> The condition was associated with cutaneous hyperreactivity to intradermal injections of ragweed and other pollen extracts, and this hyperreactivity could be passively transferred by the injection of serum to other dogs and to humans. Subsequent work by Wittich and other investigators further characterized the syndrome, eventually resulting in the determination that the relevant serum factor was, in fact, the canine equivalent

of immunoglobulin E (IgE).<sup>2–4</sup> This condition was then termed canine atopic dermatitis (AD).

## Is canine AD the same as human AD?

Canine AD shares a number of features with human AD. Humans and dogs are often hypersensitive to the same allergen sources, if not always to identical specific allergens.<sup>5</sup> In both species, the condition usually begins early in life, although the canine variant typically starts at the equivalent of adolescence or early adulthood, in contrast to humans, who are typically first affected in infancy.<sup>6,7</sup> The two conditions are phenotypically similar, with both species demonstrating a predilection for lesional distribution on the face, flexural skin, and distal extremities (See [Figures 1 and 2](#)).<sup>6,8</sup>

Although there are many similarities between canine and human AD, there are also significant differences between the

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**Fig. 1** Canine atopic dermatitis, acute lesions. This dog demonstrates erythema, excoriation and partial alopecia on the skin of the distal extremities and in the axillary and antecubital fold regions.

two disorders, which suggests that they may not be completely analogous:

1. Total serum IgE levels appear to have no clinical relevance in the dog, although allergen specific IgE does often correlate with clinical disease.
2. Although multiple-organ hypersensitivity syndromes can occur in dogs with AD, as they do in humans, there is no evidence of an “atopic march”—like pattern of progressive, sequential acquisition of systemic hypersensitivity disorders in the dog.
3. Although dogs with AD do appear to suffer from epidermal barrier derangement, there is no significant association with mutations in filaggrin.
4. Finally, treatment of canine AD differs from that of the human condition in the lesser emphasis on topical therapy and the inclusion of allergen specific immunotherapy (ASIT) as a major element in long-term disease control.

### The role of IgE in canine AD

In humans with AD, total (and often allergen-specific) IgE levels are elevated in the most common variant of the disease (“extrinsic AD”).<sup>9,10</sup> Total IgE levels are considerably higher even in normal dogs than in humans (1-41  $\mu\text{g/mL}$  and  $<130 \text{ U/mL}$  [ $\sim 317.2 \text{ ng/mL}$ ], respectively).<sup>11,12</sup> The reason for this difference is uncertain; the levels do not differ significantly between dogs with and without detectable parasitism<sup>13</sup>; furthermore, there is considerable evidence that total IgE levels do not correspond with the atopic status or severity in dogs but may correlate better with breed and neutering status.<sup>13–15</sup>

In contrast, allergen-specific IgE levels are more strongly associated with the presence of canine allergic skin disease. Specific IgE levels increase after allergen challenge in dogs, and serum IgE and intradermal test reactivities are commonly used as a diagnostic tool to help identify relevant



**Fig. 2** Canine atopic dermatitis, chronic lesions. This dog demonstrates erythema, lichenification and alopecia primarily affecting the skin of the face, distal extremities and flexural areas.

allergens in affected dogs.<sup>16,17</sup> IgE has been found on the surface of Langerhans cells in the epidermis of atopic (but not atopic) dogs, and positive environmental allergen patch tests have only been reported in dogs with IgE specific to the applied allergen<sup>18,19</sup>; nonetheless, as in humans, specific IgE levels do not always correlate with clinical disease.

Complicating the interpretation of this work is the existence of an appreciable number of dogs that meet the clinical criteria for the diagnosis of AD but in which neither allergen-specific intradermal test reactivity nor increased serum allergen-specific IgE can be found. This condition has been termed atopic-like dermatitis.<sup>20</sup> Comparisons have been made between atopic-like dermatitis and intrinsic atopic dermatitis in humans, but there is still insufficient information to determine whether canine atopic-like dermatitis is truly an analogue of intrinsic atopic dermatitis.

## The relationship of cutaneous and systemic hypersensitivity disorders in the dog

In humans, the development of AD in infancy often represents the first step in the “atopic march”—the progressive evolution from nonallergic skin disease to IgE-mediated sensitization and development of other allergic diseases, such as conjunctivitis, rhinitis, and asthma.<sup>8</sup> In contrast, there is currently insufficient evidence that a similar progression exists in the dog. It may be more relevant to ask instead whether the dog also exhibits multiple systemic hypersensitivity disorders.

### Food allergy

In children, IgE sensitization to food allergens often precedes sensitization to “typical” environmental allergens, but this sensitization appears to be of limited clinical relevance.<sup>21</sup> In contrast, evidence suggests that dogs have a predisposition to develop both food-associated dermatitis (adverse food reactions) and AD, often concurrently.<sup>22,23</sup> Canine adverse food reactions may be clinically indistinguishable from non-food associated AD (food-induced atopic dermatitis) but may also present with signs not typically associated with AD, such as steroid-resistant pruritus; therefore, it is not correct to state that adverse food reactions and food-induced atopic dermatitis are necessarily the same entity.<sup>6,24</sup>

### Conjunctivitis and rhinitis

Conjunctivitis has been reported in up to 60% of dogs with AD and is strongly associated with an allergen-specific conjunctival provocation test.<sup>25,26</sup> Rhinitis appears to be less common and has been reported in up to 11% of dogs with AD.<sup>6,25</sup>

## Asthma and lower respiratory disease

Dogs are not generally considered to spontaneously develop an “asthmatic” phenotype, although many of the earliest reports of canine “atopy” described spontaneous “asthmatic attacks” and “hay fever,” with or without allergic dermatitis.<sup>1,2</sup> Subsequent studies have reported that dogs will readily develop airway hyperactivity after experimental sensitization.<sup>27</sup> Dogs also may spontaneously develop a syndrome of eosinophilic bronchopneumonopathy.<sup>28</sup> This condition initially presents with coughing and may progress to dyspnea and exercise intolerance (occasionally in association with pruritus).<sup>28</sup> Whether this syndrome represents a canine variant of asthma remains unknown.

## Epidermal barrier defects and canine AD

In humans, the presence of epidermal barrier defects strongly correlates with the development of AD, allergic rhinitis, food allergy, and asthma.<sup>29</sup> This is particularly true for mutations in filaggrin, but defects in other barrier components (serine protease inhibitor Kazal-type 5 and claudin) may also be seen.<sup>9,30</sup>

There is evidence that skin barrier function is also impaired in dogs with AD. Several studies have reported increased transepidermal water loss as well as decreased epidermal ceramide levels and increased epidermal cholesterol in dogs with AD.<sup>31,32</sup> Electron microscopic studies have found disorganization and lack of continuity in epidermal lipid lamellae in dogs with AD, and this disorganization has been reported to worsen after allergen challenge.<sup>33</sup>

In contrast to humans, several gene association studies have failed to find a significant association between canine AD and filaggrin mutations, although an association was made in a very limited population (specifically, British Labrador retrievers).<sup>34</sup> Abnormalities in filaggrin mRNA and protein expression have been reported in dogs with spontaneous and experimentally induced AD.<sup>35</sup> The evidence for abnormal expression of other epidermal barrier components is not as clear; studies investigating the expression of claudin-1, ZO-1, and occludin have yielded conflicting results.<sup>36–38</sup>

## Clinical management of canine AD

Many of the therapeutic modalities used to manage AD in humans are also used to control clinical signs in dogs with AD. In both species, effective management requires a multimodal approach, in which treatment of atopic “flares” is combined with long-term therapy for management of chronic disease.<sup>39–42</sup> Pruritus in both species tends to be relatively responsive to systemic glucocorticoids (at least initially), although long-term usage is to be avoided, whenever possible.<sup>41</sup> Systemic immunomodulators, such as

calcineurin inhibitors (cyclosporine), have also been used with good success.<sup>41</sup>

Despite these similarities, there are also significant differences in the basic approach to management of human and canine AD. Two of the areas in which management differs the most are topical therapy and allergen-specific immunotherapy (ASIT).

### Topical therapy

Topical therapy represents the mainstay of treatment for management of AD in humans.<sup>40</sup> Topical glucocorticoids are very useful in controlling the pruritus associated with flares of AD, and proactive intermittent application protocols significantly decrease the number of flares with minimal medication-associated morbidity.<sup>40</sup> Other topical treatments include the calcineurin inhibitors tacrolimus and pimecrolimus.<sup>40</sup>

Unfortunately, the utility of most forms of topical therapy in the management of canine AD is limited by a number of factors. First, application of many forms of topical medications (lotions, creams, ointments) is difficult due to the dense pelage of most breeds of dog. Although this factor can be minimized by close clipping, this approach is often rejected by dog owners. Second, although other forms of topical therapy (bathing, application of moisturizing or humectant agents) can more easily be used, many clients are unable or unwilling to bathe their dogs on more than an occasional basis. Finally, the effectiveness of topical medication application is decreased by the tendency of the patient to remove the product by licking, although this can be minimized by temporarily placing the dog in a restrictive collar.

Although many clients find bathing their dogs to be difficult, frequent baths may decrease both pruritus and the frequency and severity of infection with *Staphylococcus* and *Malassezia spp.*<sup>39</sup> If skin dryness is a problem, baths may be followed by the application of moisturizing products or sprays. Spray formulations of glucocorticoids (such as triamcinolone or hydrocortisone aceponate) may provide effective control of focal pruritus, although patients must be monitored for the development of cutaneous atrophy.<sup>39</sup> Topical tacrolimus is expensive but may be useful for control of focal pruritus when skin atrophy becomes a problem.<sup>39</sup> As in humans, proactive intermittent application of topical glucocorticoids or tacrolimus may increase the time between atopy flares.

### Allergen specific immunotherapy

Allergy testing (either by *in vitro* analysis of allergen specific IgE or by *in vivo* allergen challenge techniques, such as skin prick testing) is generally not performed in humans with AD, although these modalities are commonly incorporated into the management of other allergic diseases, such as rhinitis or asthma.<sup>42,43</sup>

In contrast, allergy testing and ASIT play a major role in long-term management of the atopic dog. *In vivo* allergen challenge by intradermal allergen injection is generally

assumed to be the “gold standard” because this assay provides functional evidence of hyperreactivity. More recently, *in vitro* assessment of allergen-specific IgE has become a valid diagnostic alternative.<sup>17</sup> Unfortunately, there is currently no standardization in the performance of either type of assay, and the results of serologic tests may vary substantially between laboratories.<sup>44</sup>

Despite these limitations, ASIT remains a very effective tool for the long-term modification of canine AD. Several retrospective surveys have determined that ASIT can produce significant improvements in both client- and clinician-oriented parameters in up to 70% of dogs.<sup>45</sup> Response is not instantaneous, and patients may not experience clinical benefit for up to a year. Administration of ASIT to dogs has traditionally been performed by subcutaneous injection, but sublingual immunotherapy may also be considered.<sup>46</sup>

### Conclusions

Domestic dogs can develop a syndrome of spontaneous cutaneous hypersensitivity that shares a number of features with human AD, including lesion distribution and young age of onset. Affected individuals of both species typically develop allergen-specific IgE directed against allergens from common environmental sources, such as those derived from pollens and house dust mites; furthermore, there is evidence to suggest that, as in humans, dogs with AD may suffer from concurrent hypersensitivity disorders of other organ systems, such as conjunctivitis and rhinitis.

Although there are many similarities between canine and human AD, there are also significant differences. Total serum IgE levels appear to have no clinical relevance in the dog. Although dogs with AD do appear to suffer from epidermal barrier derangement, there is no association with mutations of filaggrin. Dogs also do not appear to have a predictable “atopic march.” Finally, treatment of canine AD differs from that of the human condition in the lesser emphasis on topical therapy and the inclusion of ASIT as a major element in long-term disease control.

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