Canine atopic dermatitis is a complex multifactorial disease. Here, Tim Nuttall, Maarja Uri and Richard Halliwell, representing three generations of veterinary dermatologists, describe the research underpinning our understanding of the condition and highlight its relevance to clinical practice.

Defining canine atopic dermatitis – then and now

Canine atopic dermatitis was originally thought of as an allergic inhalant dermatitis. Better understanding of the epidemiology, immunology and clinical signs led to the definition of atopic dermatitis as a ‘genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE, most commonly directed against environmental allergens’ (Halliwell 2006). However, it was also recognised that canine atopic dermatitis is a complex and multifactorial disease involving immune dysregulation, allergic sensitisation, skin barrier defects, microbial colonisation and environmental factors. IgE is not a prerequisite for the development of the clinical signs in all cases, and a separate clinical entity known as atopic-like dermatitis was defined as ‘an inflammatory and pruritic skin disease with clinical features identical to those seen in canine atopic dermatitis in which an IgE response to environmental or other allergens cannot be documented’. The term ‘food-induced allergic dermatitis’ is used to distinguish cases in which food allergens may trigger a flare from non-food induced atopic dermatitis or canine atopic dermatitis senso strictu (Olivry and others 2007, Picco and others 2008).

Clinical signs and diagnosis

It is widely accepted that the history and clinical signs are important in the diagnosis of canine atopic dermatitis. However, it was not until 1986 that Ton Willemse first proposed a set of diagnostic criteria (Willemse 1986). These criteria were widely used, although they were never fully validated. Pascal Prélaud and colleagues later revised these to improve the specificity for canine atopic dermatitis (Prelaud and others 1998). Prélaud’s criteria were validated, but the sample size was small and limited to France. It was not until 2010 that Favrot and colleagues published a robust set of historical and clinical criteria consistent with a diagnosis of canine atopic dermatitis (Box 1). This study analysed data from over 1500 dogs from 15 countries in Europe, the Americas and Asia. Favrot
and others’ criteria are now extensively used to support the diagnosis of canine atopic dermatitis, especially in clinical trials and other studies where it is important to include a homogenous study population. However, it has also been shown that there are significant breed variations in the history and clinical presentation of canine atopic dermatitis (Box 2). It is therefore important to note that none of the criteria is pathognomonic, and simply following these would lead to an incorrect diagnosis in every fifth to sixth dog. Canine atopic dermatitis therefore still remains a diagnosis of exclusion, and it is essential to eliminate ectoparasites and evaluate the role of food.

Genetic background
Canine atopic dermatitis is very common with up to 10 per cent of dogs affected worldwide (Lund and others 1999, Hillier and others 2001, Scott and others 2001). There are a number of widely recognised breed associations suggesting that atopic dermatitis is a genetically mediated familial condition. Zur and colleagues (2002) in the USA showed that labradors and golden retrievers, West Highland white terriers, English springer spaniels, Chinese shar peis, bull terriers, bichon frise and Tibetan terriers were statistically more likely to present with atopic dermatitis, whereas mixed-breed dogs had a lower than expected prevalence. The breed prevalence elsewhere is similar, although it can vary between geographical locations – predisposed breeds in Switzerland, for example, include West Highland white terriers, boxers, French bulldogs, Hungarian viztatas, bull terriers, Rhodian ridgebacks and basset hounds (Picco and others 2008). In British guide dogs (mostly labrador and golden retriever crosses) the heritability is 0.47, meaning that nearly 50 per cent of the risk of developing atopic dermatitis can be accounted for by their genotype (Shaw and others 2004). The genetic background, however, is likely to involve multiple genes and complex interactions between skin structure, the immune system and the environment.

The genomics revolution has greatly contributed to our knowledge of canine atopic dermatitis. Microarray studies have shown that a large number of genes are differentially expressed in canine atopic dermatitis (Merryman-Simpson and others 2008, Wood and others 2009a, Pfager and others 2012). These include genes associated with altered IgE function, mediators associated with inflammation and immunity, cell messaging pathways, epidermal barrier function, oxidative damage repair, and apoptosis and cell cycle regulation. Genome-wide linkage and genome-wide association studies have identified a number of atopic dermatitis-associated abnormalities, but these vary between breeds and different geographical locations (Wood and others 2009b, 2010, Roque and others 2011, 2012, Salzmann and others 2011).

The genetic background to canine atopic dermatitis probably varies between breeds and gene pools. This could explain variations in clinical phenotype and response to treatment. This complex genetic background makes it unlikely that genetic tests and breeding programmes to eliminate the disease will be successful. Nevertheless, understanding the genotype will help to identify key triggers and novel treatments. Genotyping may allow us to select more effective treatments or suggest environmental intervention for at-risk individuals to prevent the disease developing later in life.

Does the environment influence atopic dermatitis?
There is a strong genetic component to canine atopic dermatitis but this does not explain all the risk and environmental factors that are likely to be important. The hygiene hypothesis speculates that early exposure to microorganisms is important in the maturation of tolerance. Certain risk factors for canine atopic dermatitis are consistent with this hypothesis (Nordvedt and others 2007a, b, Picco and others 2008, Meury and others 2011, van Beck and others 2011) (Table 1). Early exposure to the probiotic Lactobacillus rhamnosus in an experimental beagle model significantly decreased...
allergen-specific IgE and partially prevented atopic dermatitis in the first six months of life but was not consistently beneficial (Manella and others 2012). Again, however, there is breed variation; for example, atopic dermatitis in West Highland white terriers is not correlated with environmental factors (Picco and others 2008).

**An outside-in dermatitis? Skin barrier function**

It is now thought that altered skin barrier function plays an important role in the pathogenesis of canine atopic dermatitis (Marsella and others 2011). Regular bathing, which may disrupt the skin barrier, is a risk factor for atopic dermatitis (Picco and others 2008), and tape-stripping of Maltese-beagle atopic dogs enhanced *Dermatophagoides farinae* allergen-specific responses compared to non-treated controls (Olivry and others 2011). Furthermore, transepidermal water loss is higher in atopic beagles than in healthy controls (Marsella and Samuelson 2009, Hightower and others 2010). Other studies have shown changes in the stratum corneum, the epidermal lipid layer, and in ceramide profiles in atopic compared to healthy dogs (Piekutowska and others 2008), Reiter and others 2009, Shimada and others 2009, Marsella and others 2010, Popa and others 2011). Altered filaggrin (which is essential for skin barrier function and is strongly associated with human atopic dermatitis) expression and loss-of-function mutations have also been associated with canine atopic dermatitis (Marsella and others 2009, Cherif and others 2010). However, there are again breed differences; for example, filaggrin gene mutations have been associated with atopic dermatitis in British labrador retrievers (Wood and others 2010, Salzmann and others 2011, Roque and others 2012) and Thai small breed dogs (Suriyaphol and others 2011) but not in West Highland white terriers (Wood and others 2010, Salzmann and others 2011, Roque and others 2012). Recent studies have shown that some of the changes to the epidermal lipid layer can be reversed using oral n3 fatty acids and a topical skin lipid layer can be reversed using oral n3 and a topical skin lipid layer (Picco and others 2011) but not in West Highland white terriers (Wood and others 2010, Salzmann and others 2011, Roque and others 2012). Rather than reflecting a TH2/TH1 imbalance, canine atopic dermatitis appears to show a progression from early humoral TH2-type inflammation to chronic TH1-type cell-mediated inflammation. This may be associated with a failure of regulation, as studies have demonstrated altered T regulatory (Treg) cell and immunoregulatory cytokine function (particularly transforming growth factor-β1 and interleukin (IL) 10) in canine atopic dermatitis (Hayashiya and others 2002, Nuttall and others 2002, Maeda and others 2005, 2008). However, it was subsequently demonstrated that there is a TH1-dominant pattern, which mediates cellular mediated inflammation, in chronic lesions (Olivry and others 1999a, Nuttall and others 2002, 2004, 2005, 2008). Rather than reflecting a TH2/TH1 imbalance, canine atopic dermatitis appears to show a progression from early humoral TH2-type inflammation to chronic TH1-type cell-mediated inflammation. This may be associated with a failure of regulation, as studies have demonstrated altered T regulatory (Treg) cell and immunoregulatory cytokine function (particularly transforming growth factor-β1 and interleukin (IL) 10) in canine atopic dermatitis (Hayashiya and others 2002, Nuttall and others 2002, Maeda and others 2007). Furthermore, successful allergen-specific immunotherapy

**What’s happening in the skin? Cell, cytokine and chemokine profiles**

Early studies were limited to phenotyping cellular infiltration and histopathological changes in atopic skin. Non-lesional atopic skin is characterised by mild epidermal spongiosis with sparse superficial perivascular infiltrates of lymphocytes, monocytes, dendritic cells and mast cells (Fig 2a) (Olivry and others 1997, 1999b, Marsella and others 2006b). In lesional skin, there is progressive epidermal spongiosis, acanthosis and hyperkeratosis, and infiltration of CD4+ and CD8+ T cells, monocytes, eosinophils, neutrophils, mast cells and plasma cells (Fig 2b). The key role of the mast cell was recognised early. Allergen exposure triggers the release of preformed and stored mediators that initiate immediate phase inflammatory responses and late phase reactions. Mast cells concentrate in the pinnae, ventral and interdigital skin (Auxilia and Hill 2000), which are all predilection sites for atopic dermatitis. Mast cells express the high affinity IgE receptor FcεRI, which enables stable binding of IgE in the skin and increases the sensitivity of allergen-mediated activation (Zeman and others 2002). IgE binding to FcεRI on epidermal Langerhans’ cells also increases the efficiency of allergen presentation. The presence of FcεRI allows atopic dogs to become sensitised and react to trace amounts of allergen.

Advances in molecular biology have allowed more recent studies to look beyond the cells and investigate the cytokine milieu in canine atopic dermatitis. This has greatly increased our understanding of the disease, and led to new approaches to treatment. Initially, canine atopic dermatitis was assumed to be a T helper 2 (TH2)-associated disease, as TH2 responses mediate IgE production and allergic reactions (Olivry and others 1999a, Hayashiya and others 2002, Maeda and others 2002, 2004, 2005, Nuttall and others 2002, Pucheu-Haston and others 2006, 2008). However, it was subsequently demonstrated that there is a TH1-dominant pattern, which mediates cellular mediated inflammation, in chronic lesions (Olivry and others 1999a, Nuttall and others 2002, 2004, Maeda and others 2005, 2008, Pucheu-Haston and others 2006, 2008). Rather than reflecting a TH2/TH1 imbalance, canine atopic dermatitis appears to show a progression from early humoral TH2-type inflammation to chronic TH1-type cell mediated inflammation. This may be associated with a failure of regulation, as studies have demonstrated altered T regulatory (Treg) cell and immunoregulatory cytokine function (particularly transforming growth factor-β1 and interleukin (IL) 10) in canine atopic dermatitis (Hayashiya and others 2002, Nuttall and others 2002, Maeda and others 2007). Furthermore, successful allergen-specific immunotherapy

![FIG 2: (a) Histopathology of non-lesional atopic skin. This skin is not normal; there is mild epidermal spongiosis with a sparse superficial perivascular infiltrate of lymphocytes and other monocytes. This shows why regular ongoing treatment of affected dogs is important even if they look clinically healthy. (b) Histopathology of lesional atopic skin, with severe epidermal spongiosis, acanthosis and hyperkeratosis, and infiltration of lymphocytes, monocytes, eosinophils, neutrophils, mast cells and plasma cells. This dog needs specific anti-inflammatory treatment to resolve the inflammation; simple emollients or allergen-specific immunotherapy will not be effective in these cases. Haematoxylin and eosin. x 400](Image 217x651 to 389x787)

| TABLE 1: Suspected environmental factors that may be associated with the development of canine atopic dermatitis (Nodtvedt and others 2007a, b, Picco and others 2008, Meury and others 2011, van Beeck and others 2011) |
|-------------------------------------------------|-----------------------------|
| Risk of developing atopic dermatitis | Environmental factor |
| Increased | Urban life | High human population density | Increased average annual rainfall | Adoption at the age of 8 to 12 weeks |
| Reduced | Rural life | Living with other animals | Walking in forests | Feeding non-commercial foods to lactating bitches |
| No effect | Sex | Season of birth | Home environment | Vaccination | De-worming |
has been associated with FoxP3+, CD4+, Treg cells and IL-10 levels (Keppel and others 2005). Very recently, the role of neuronal stimulators, particular IL-31, in the pathogenesis of pruritus has been discovered (McCandless and others 2012, Gonzales and others 2013). IL-31 has been associated with canine atopic dermatitis, and injection of recombinant IL-31 induces pruritus in normal dogs. In addition, the specific Janus kinase inhibitor, oclacitinib, reduces pruritus by blocking IL-31 signals (Cosgrove and others 2012) (Table 2).

IgE responses to environmental allergens

Dogs with atopic dermatitis are sensitised to environmental allergens (Fig 3). Early studies demonstrated this using intradermal allergens and passive transfer tests (Burns 1933, Schnelle 1933, Romeroy 1934, Wittich 1941, Schwartzman 1965). The isolation and identification of canine IgE by Richard Halliwell and colleagues was a key breakthrough (Halliwell and others 1972, 1975, Halliwell 1973). Serological tests for allergen-specific IgE are now widely used in laboratory research and clinical practice. This has greatly improved access to allergen testing and allergen-specific immunotherapy. However, positive tests are not specific for canine atopic dermatitis and cannot be used to confirm the diagnosis (Codner and Tinker 1995, Lian and Halliwell 1998).

Instead, allergen-specific tests are used to identify allergens for avoidance and for inclusion in allergen-specific immunotherapy following a clinical diagnosis of canine atopic dermatitis. Allergen-specific immunotherapy is a safe and effective way to manage relapses associated with exposure to allergens (Loewenstein and Mueller 2009). It is not, however, an anti-inflammatory treatment—short-term to medium-term anti-inflammatory therapy is almost always required to reverse chronic inflammatory changes.

The most commonly implicated allergens are the *Dematophagoides* species house dust mites (Hill and DeBoer 2001). Intradermal test reactivity, IgE serology, passive transfer tests, T cell proliferation tests, basophil degranulation tests, responses to specific immunotherapy, and amelioration and exacerbation following avoidance and exposure (reviewed in Nuttall and others 2006) show that *Dermatophagoides* are directly relevant to canine atopic dermatitis. Specific allergenic proteins (Der f1 and Der f10) have also been identified (McCall and others 2000, Weber and others 2001). Similar studies performed with Japanese cedar (*Cryptomeria japonica*) have identified three allergenic proteins, Cry 1, Cry 2 and Cry 3 (Masuda and others 2006, Kubota and others 2012).

It is therefore clear that sensitisation to these allergens plays a role in the pathogenesis of canine atopic dermatitis. Unfortunately, this association has not been made for other allergens, and their role remains speculative. False-positive tests can occur, and it is important that clinicians relate positive tests to likely exposure. In particular, pollen exposure should match seasonal disease or seasonal exacerbation in pollen-sensitive dogs. A very recent study showed that most dogs reacted to multiple allergens from related groups (Buckley and others 2012). This suggests that there is either extensive cross-reaction or co-sensitisation between related allergens. Further studies are needed to differentiate this, but it may be possible to simplify testing and immunotherapy in the future by using key cross-reacting allergens or allergen mixes.

However, as discussed, other factors are important in the pathogenesis of canine atopic dermatitis. It is unclear whether allergen sensitisation plays a primary role or whether it is secondary to altered skin barrier function and abnormal cutaneous immunity. In either case, epicutaneous allergen exposure is most important; oral and inhalation exposure resulted in less severe and more transient clinical lesions, although multiple routes of exposure were additive (Mansella and others 2006a). Interestingly, lesion distribution is not affected by the route of exposure and closely matches that expected in clinical atopic dermatitis, with lesions occurring in covered skin. Allergens may also directly affect the skin barrier; a recent study showed that cutaneous application of *Dermatophagoides* extract reduced ceramide levels, potentially compromising skin barrier function at the application site and adjacent skin (Stahl and others 2012).

Role of microbial colonisation

The development of chronic lesions in canine atopic dermatitis is often associated with secondary microbial infection with *Malassezia* or staphylococci. Staphylococcal carriage is higher in atopic dogs than in healthy dogs or atopic dogs in remission, with almost all atopic dogs colonised with *Staphylococcus pseudintermedius* (Harvey and Noble 1994, Fazakerley and others 2009). *S. pseudintermedius* adheres more readily to the skin (stahl and others 2012). carriage is higher in atopic dogs than in healthy dogs or atopic dogs in remission, with almost all atopic dogs colonised with *Staphylococcus pseudintermedius* (Harvey and Noble 1994, Fazakerley and others 2009). *S. pseudintermedius* adheres more readily to both non-lesional and lesional atopic canine skin compared to healthy skin (McEwan 2000, McEwan and others 2005, Simou and others 2005). It is now thought that colonisation and infection is associated with host factors. Recent studies have focused on β-defensins (which are important antimicrobial peptides found in the skin and mucosa) activity, but findings have not
Evidence-based medicine in canine atopic dermatitis

Dermatology was one of the first veterinary disciplines to embrace evidence-based medicine. ITTCAD and later ICADA groups reviewed the literature to identify clinical trials for therapeutic interventions in canine atopic dermatitis. These were evaluated for quality and efficacy to produce recommendations for treatment (Box 3). Clinicians in first-opinion practice will rarely have the time to individually analyse clinical trials, and these meta-analyses are an ideal way to access the high-quality data and recommendations needed to make evidence-based clinical decisions. The results from these analyses were recently summarised in the 2010 ICADA Guidelines for the Treatment of Canine Atopic Dermatitis (Box 4) (an open-access article and freely available in a number of different languages).

Groups have also been working to improve the quality of clinical trials and facilitate comparison between studies. For example, it is now expected that clinical trials will report validated clinical lesion and pruritus scores (Hill and others 2007, Olivry and others 2007). More recently, a quality of life score has been validated (Favrot and others 2010). This represents a major advance in assessing clinical trials, as quality of life is probably the most important outcome measure for affected dogs and their owners (Linek and Favrot 2010).

Relevance to veterinary practice

We can only provide a short overview of the huge advances that have been made in understanding the pathogenesis, diagnosis and treatment of canine atopic dermatitis. However, there are a number of key findings that are directly relevant to clinical practice:

- Canine atopic dermatitis is a genetically mediated disease. Owners should be advised about the consequences of breeding from affected dogs.
- Canine allergic dermatitis may be associated with reactions to food as well as environmental allergens. Food trials should be part of the investigation in all cases, and avoidance of food allergens may be important in some dogs.
- Canine atopic dermatitis is associated with characteristic historical features and clinical signs, but these are not absolutely specific and other pruritic dermatoses must be eliminated to confirm the diagnosis.
- Canine atopic dermatitis is more than an allergic disease. Canine atopic dermatitis is a complex multifactorial disease involving flare factors, a poor skin barrier, allergic sensitisation and cutaneous inflammation; all of these factors should be addressed for successful long-term treatment.
- Canine atopic dermatitis is a variable disease. There is breed and individual variation in clinical signs and response to treatment; every dog should be treated as an individual, and no one treatment is likely to be successful in all cases.
- Canine atopic dermatitis is a lifelong disease. The best results are associated with consistent ongoing treatment that keeps the clinical signs in remission.
- Canine atopic dermatitis has a complex and dynamic pattern of cytokine expression involving TH2, TH1 and immunoregulatory cytokines. Atopic skin exhibits chronic relapsing inflammation, which is best managed with consistent proactive treatment, whether or not the skin looks normal, rather than reactively treating flares of inflammation.

Box 3: Evidence-based medicine recommendations for the treatment of canine atopic dermatitis (Olivry and Mueller 2003, Olivry and others 2010b, Olivry and Bizikova 2013)

<table>
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<tr>
<th>High quality evidence</th>
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<tr>
<td>Oral glucocorticoids</td>
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<td>Oral ciclosporin</td>
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<th>Moderate quality evidence</th>
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<tr>
<td>Subcutaneous allergen-specific immunotherapy</td>
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<td>Topical hydrocortisone aceponate</td>
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<td>Topical tacrolimus</td>
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<td>Oral essential fatty acids (as a steroid sparing agent)</td>
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<td>Oral Chinese herbal therapy (as a steroid sparing agent)</td>
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<td>Oral pentoxifyline</td>
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<th>Low quality evidence</th>
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<tr>
<td>Injectable interferon omega</td>
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<td>Budesonide leave-on conditioner</td>
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<td>Topical ciclosporin nano-emulsion</td>
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<td>Oral fexofenadine</td>
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<td>Oral mexitelinn</td>
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<td>Essential fatty acid containing diets</td>
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<tr>
<td>Topical hydrocortisone aceponate (as intermittent therapy on two days/ week)</td>
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Box 4: Key recommendations from the 2010 ICADA Guidelines for the Treatment of Atopic Dermatitis (Olivry and others 2010a)

### Treatment of acute flares of atopic dermatitis

- Avoidance of flare factors:
  - Regular flea control
  - Evaluation of the role of food allergens
  - Identification and avoidance of environmental factors (eg, temperature, humidity, irritants and allergens)
  - Identification and treatment of secondary staphylococcal and Malassezia infections
  - Bathing with emollient and anti-pruritic shampoos (eg, Allermyl; Virbac Animal Health)
  - Topical glucocorticoids (eg, hydrocortisone aceponate or triamcinolone)
  - Oral glucocorticoids

### Treatment of chronic atopic dermatitis

- Avoidance of flare factors:
  - Regular flea control
  - Evaluation of the role of food allergens
  - Identification and avoidance of environmental factors (eg, temperature, humidity, irritants and allergens)
  - Identification and treatment of secondary staphylococcal and Malassezia infections
  - Bathing with emollient and anti-pruritic shampoos
  - Dietary supplementation with essential fatty acids or feeding essential fatty acid enriched diets
  - Topical glucocorticoids (eg, hydrocortisone aceponate or triamcinolone)
  - Oral ciclosporin

- Allergen-specific immunotherapy:
  - To prevent future flares associated with allergen exposure, ie, to induce tolerance to environmental allergens
Allergen-specific immunotherapy is safe and effective. Allergen testing and immunotherapy should be considered in all cases.

Atopic skin is readily colonized by staphylococci and Malassezia. Secondary infections should promptly identified and treated.

Use evidence-based medicine for clinical decision-making. Meta-analyses have identified the most effective therapeutic interventions, and these have been brought together in clinical guidelines.

Conclusion

There have been great changes in our understanding of canine atopic dermatitis in the past 75 years. There have been huge advances in diagnosis and management, but canine atopic dermatitis remains a clinical challenge. It is a very common and very distressing condition that causes undoubted challenge. It is a very common and very frustrating for their owners and clinicians. Nevertheless, we are confident that ongoing research will continue to reveal its mysteries and lead to safer and more efficacious forms of treatment.

References


MARSELLA, R., NICKLIN, C. R. & LOPEZ, J. (2006a) Studies on the role of routes of allergen exposure in high-IgE producing beagle dogs sensitized to house dust mites. Veterinary Research 37, 301-308.


