Feature

Veterinary Record 125 years

SMALL ANIMAL DERMATOLOGY

Canine atopic dermatitis – what have we learned?

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.

CONDITIONS that we would now regard as atopic dermatitis (Fig 1) have long been recognised in dogs. It was first shown that dogs suffer from allergic 'eczema' in the 1930s, although these early studies were limited to food allergens (Burns 1933, Schnelle 1933, Pomeroy 1934). Wittich published the first really detailed description in 1941 when he reported a case of 'spontaneous allergy (atopy)' in a dog with rhinitis, conjunctivitis and urticaria (Wittich 1941). He was able to demonstrate allergic sensitisation to ragweed pollen and a response to allergen-specific immunotherapy (ASIT). Further studies suggested that pollen exposure could induce the formation of allergen-specific antibodies, and that subsequent allergen exposure could result in atopic conjunctivitis, rhinitis, asthma, pruritus and anaphylaxis, although not what we would now regard as canine atopic dermatitis. Schwartzman and colleagues first linked respiratory disease and pruritus with the diagnosis of 'atopy' (Schwartzman 1965). They proposed that atopic dogs became sensitised following inhalation of allergens. The allergen-specific IgE would then bind to mast cells, triggering the release of histamine and other mediators following subsequent allergen exposure.

This 'allergen-centric' view of canine atopic dermatitis persisted for many years, but gradually our understanding of the condition has changed. Numerous studies published since the 1970s have greatly expanded our knowledge of canine atopic dermatitis. In 2001, an American College of Veterinary Dermatology task force collated the first comprehensive review of the clinical features, immunology and management of canine atopic dermatitis. This group evolved into the International Task Force for Canine Atopic Dermatitis (ITFCAD), which later became the International Committee for Allergic Diseases in Animals (ICADA). ICADA subcommittees continue to coordinate and review scientific and clinical research into pathogenesis, clinical diagnosis, allergy testing, allergen-specific immunotherapy and evidence-based treatment guidelines. Here we will briefly summarise what has been achieved, and how research findings are relevant to clinical practice.

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Veterinary Record is 125 years old this year. To celebrate, we are publishing an article each month focusing on a key clinical topic. Each article aims to look at what the challenges have been, how the topic has developed and what the future might hold. The first article, on cattle lameness, appeared in *VR*, January 26, 2013, pp 92-95.

(right) The first issue of *Veterinary Record*, published on July 14, 1888, and how it looks today

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 (Prélaud 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

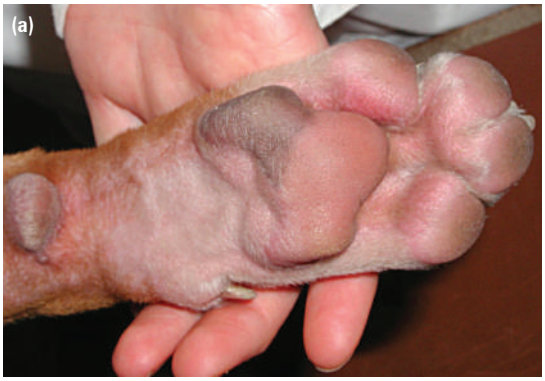

FIG 1: (a) Early atopic dermatitis in a pruritic Staffordshire bull terrier. There is diffuse erythema of the plantar metacarpal and interdigital skin, but the dog had few other lesions. (b) Chronic atopic dermatitis in a German shepherd dog. In this case the original presentation has been complicated by extensive chronic cell-mediated inflammation associated with alopecia, lichenification and hyperpigmentation. This dog also had a severe secondary *Malassezia* dermatitis

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 Griffin 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 labrador and golden retrievers, West Highland white terriers, English springer spaniels, Chinese shar peis, bull terriers, bichon frisé 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 vizslas, bull terriers, Rhodesian 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, Plager 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 (Nodtvedt and others 2007a, b, Picco and others 2008, Meury and others 2011, van Beeck and others 2011) (Table 1). Early exposure to the probiotic *Lactobacillus rhamnosus* in an experimental beagle model significantly decreased

Box 1: Historical and clinical criteria consistent with a diagnosis of canine atopic dermatitis (Favrot and others 2010b)

- Onset of signs under three years of age
- Dog living mostly indoors
- Glucocorticoid-responsive pruritus
- Pruritus before skin lesions
- Affected front feet and concave (ie, inner) surface of the ear pinnae
- Non-affected ear margins (affected ear margins most consistent with *Sarcoptes*)
- Non-affected dorsolumbar area (affected dorsolumbar area most consistent with flea allergic dermatitis)

Box 2: Affected sites and clinical features that are more likely to be seen in certain breeds with canine atopic dermatitis (Wilhelm and others 2011)

- Dalmatian: lips; and/or pruritus without lesions
- French bulldog: axillae, eyelids and flexor surfaces
- German shepherd dog: elbows, hindlimbs and thorax; seborrhoea; generalised disease; and/or pruritus without lesions
- Shar pei: thorax, hindlimbs, flexor surfaces and dorsolumbar skin; and/or pruritus without lesions
- West Highland white terrier: dorsolumbar skin, feet, flexor surfaces, lips, face and genitals; seborrhoea; *Malassezia* dermatitis; and/or generalised disease
- Boxer: urticaria and otitis
- Labrador retriever: dry skin

allergen-specific IgE and partially prevented atopic dermatitis in the first six months of life but was not consistently beneficial (Marsella 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, Chervet 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 and n6 essential fatty acids and a topical skin lipid complex (Popa and others 2011, 2012), suggesting that improving the skin barrier is important in treatment.

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.

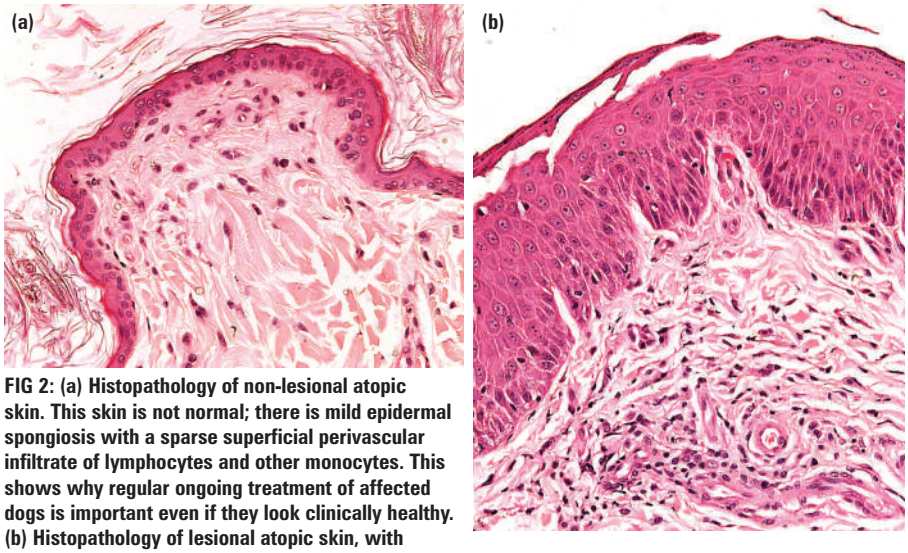

FIG 2: (a) Histopathology of non-lesional atopic skin. This skin is not normal; there is mild epidermal spongiosis with a sparse superficial perivascular infiltrate of lymphocytes and other monocytes. This shows why regular ongoing treatment of affected dogs is important even if they look clinically 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

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 cell 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

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
	Regular bathing of young healthy dogs
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

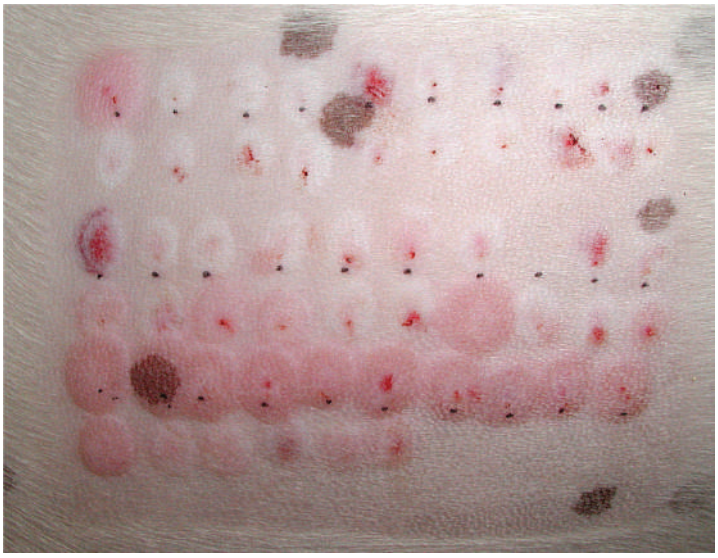

FIG 3: Intradermal allergen test in an atopic boxer dog. Histamine, the positive control, is at the top left of the test area. This dog was positive to grass pollens. Positive allergen tests should not be relied on by themselves to make a diagnosis of canine atopic dermatitis – this should be based on the history and clinical signs and exclusion of other pruritic dermatoses, particularly ectoparasites and adverse food reactions. Positive tests should relate to the patient's clinical signs – this dog has seasonal pruritus that correlated with grass pollen exposure

has been associated with FoxP3+, CD4+, Treg cells and IL-10 levels (Keppel and others 2008). 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 allergen tests and passive transfer tests (Burns 1933, Schnelle 1933, Pomeroy 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- to medium-term anti-inflammatory therapy is almost always required to reverse chronic inflammatory changes.

The most commonly implicated allergens are the *Dermatophagoides* 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 f15 and Der f18) 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 j1, Cry j2 and Cry j3 (Masuda and others 2000, 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 (Marsella 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 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

TABLE 2: Cytokines and chemokines implicated in canine atopic dermatitis. Early lesions appear to be TH2-polarised, but chronic lesions exhibit a TH1-polarised or mixed pattern (Olivry and others 1999a, Hayashiya and others 2002, Maeda and others 2002, 2004, 2005, Nuttall and others 2002, 2004, Pucheu-Haston and others 2006, 2008, Gonzales and others 2013)

Cytokines and chemokines associated with acute lesions	Cytokines and chemokines associated with chronic lesions
Interleukin [IL]-4	IL-1β
IL-5	IL-2
IL-13	IL-12
IL-31	IL-31
MCP-1 (monocyte chemoattractant protein-1/CCL-2)	IFN-γ (interferon gamma)
RANTES (regulated upon activation, normal T cell expressed/CCL-5)	TNFα (tumour necrosis factor α)
TARC (thymus and activation regulated chemokine/CCL-17)	CCL28

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)

High quality evidence
- Oral glucocorticoids
- Oral ciclosporin

Moderate quality evidence
- Subcutaneous allergen-specific immunotherapy
- Topical hydrocortisone aceponate
- Topical triamcinolone
- Topical tacrolimus
- Oral essential fatty acids (as a steroid sparing agent)
- Oral Chinese herbal therapy (as a steroid sparing agent)
- Oral pentoxifylline
- Oral misoprostol

Low quality evidence
- Injectable interferon omega
- Budesonide leave-on conditioner
- Topical ciclosporin nano-emulsion
- Oral fexofenadine
- Oral mastinib
- Essential fatty acid containing diets
- Topical hydrocortisone aceponate (as intermittent therapy on two days/week)

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)
- Topical tacrolimus
- Oral glucocorticoids
- Oral ciclosporin
- Allergen-specific immunotherapy:
  - To prevent future flares associated with allergen exposure, ie, to induce tolerance to environmental allergens

been consistent (van Damme and others 2009, Fazakerley and others 2010, Santoro and others 2011, 2012, Leonard and others 2012, Mullin and others 2013). The role of antimicrobial peptides in canine atopic dermatitis is therefore still unclear and requires further study.

Microorganisms and microbial extracts are strongly proinflammatory, attracting and activating inflammatory cells and driving chronic cell-mediated immunity. Interestingly, recent research has shown that atopic dogs develop specific IgE antibodies to *Malassezia* and staphylococci (Morris and others 1998, 2002, Nuttall and Halliwell 2001, Morris and DeBoer 2003, Bexley and others 2013). The clinical significance of this is uncertain, but if microorganisms act as allergens, then specific immunotherapy could be used to ameliorate their impact.

Evidence-based medicine in canine atopic dermatitis

Dermatology was one of the first veterinary disciplines to embrace evidence-based medicine. ITFCAD 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 2010a). 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.

- Allergen-specific immunotherapy is safe and effective. Allergen testing and immunotherapy should be considered in all cases.
- Atopic skin is readily colonised 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 suffering for the affected dogs, and is 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.

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