Canine atopic dermatitis (CAD) is a prevalent, multifaceted, pruritic skin disease with a complex etiopathogenesis (Figure 1). In recent years, remarkable progress in the understanding of CAD has led to new diagnostic and therapeutic strategies.

**UPDATE ON PATHOGENESIS OF CAD**

**Not Always IgE**

Although immunoglobulin E (IgE) is an important component in atopic dermatitis (AD), recent studies have shown that AD is not always IgE-mediated. As in humans, a small subset of dogs with AD do not have detectable—by either serology or intradermal testing—allergen-specific IgE. This form of AD has been recently referred to as atopic-like dermatitis.

**Immune Dysregulation and JK Inhibition**

Immune dysregulation in the skin of atopic dogs leads to overproduction of pro-inflammatory and pruritogenic mediators, such as T-helper type-2 cytokines, including interleukins IL-4, IL-5, IL-10, and IL-13. More recently, IL-31 was shown to play a significant role in CAD, inducing inflammation and pruritus in atopic dogs via activation of Janus kinase (JK) signal transduction. This led to the development of the JK inhibitor, oclacitinib maleate (Apoquel, zoetisus.com).

**Role of Secondary Infections**

Bacterial and yeast infections are common in atopic dogs, and are important contributing factors in the pathogenesis of AD due to:

- Increased adherence to, and colonization of, atopic skin by *staphylococi*
- Evidence that staphylococcal exotoxins serve as superantigens and, thereby, augment the cutaneous inflammatory response
- Reduced production of antimicrobial peptides (eg, defensins, cathelicidins) by epidermal cells
- Bacterial and *Malassezia* hypersensitivity, which indicates a probable role for allergen-specific immunotherapy.

These findings, along with the increased incidence of bacterial resistance, have led to new strategies in antimicrobial therapy.

**Impact of Food Allergy**

Food allergy, or food-induced dermatitis, can manifest approaches for avoidance of allergen and microbial exposure, and development of novel therapies to restore or protect the skin barrier of atopic dogs.

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University of Minnesota

What is New in the Diagnosis and Management of CANINE ATOPIC DERMATITIS?

FIGURE 1. Willie, a 4-year-old Labrador retriever with AD, had severe pruritus and secondary infections at initial presentation.
clinically in some dogs as AD. For this reason, it was recently proposed to subdivide CAD into food-induced AD and nonfood-induced AD, supporting investigation of potential food allergens in atopic dogs, particularly those with year-round signs.

NEW DIAGNOSTIC CRITERIA FOR CAD
Recently, a new set of diagnostic criteria, named Favrot’s criteria (Table 1), was published, providing a framework to assist in the diagnosis of CAD. However, these criteria have several limitations:

- Not all atopic dogs fit within these criteria
- Using the criteria alone can lead to misdiagnosis of AD
- The criteria do not differentiate between patients with and without food allergies.

TABLE 1. Favrot’s Criteria* for Canine Atopic Dermatitis (Favrot et al 2010)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Diagnosis of CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected ear pinnae (but not pinnal margins)</td>
<td>85% sensitivity</td>
</tr>
<tr>
<td>Affected front feet</td>
<td>79% specificity</td>
</tr>
<tr>
<td>Age of onset &lt; 3 years</td>
<td></td>
</tr>
<tr>
<td>Chronic or recurrent yeast infections</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid-responsive pruritus</td>
<td></td>
</tr>
<tr>
<td>Mostly indoor lifestyle</td>
<td></td>
</tr>
<tr>
<td>Nonaffected dorsolumbar area</td>
<td></td>
</tr>
<tr>
<td>Pruritus without skin lesions at onset</td>
<td></td>
</tr>
</tbody>
</table>

* At least 5 positives = 85% sensitivity (miss 15%); 79% specificity (falsely diagnose 21%)

While these guidelines may streamline diagnosis of suspected CAD, diagnosis should still be based on:

1. Patient’s signalment, history, and clinical signs characteristic of AD
2. Exclusion of other similar pruritic skin conditions, including secondary infections.

Most important, allergen-specific IgE serologic and/or intradermal tests should not be used as primary diagnostic criteria.

UPDATES ON TREATMENT OF CAD
Therapeutic Approach & Evidence of Efficacy
CAD is a noncurable disease that has a detrimental impact on the quality of life of affected animals and their owners. There is no universal treatment; therefore, it is crucial to establish an effective and safe individualized multimodal treatment plan (Figure 2), as early as possible, based on the patient’s quality of life, response to therapy, potential adverse effects, owner compliance, and medication costs (Figure 3).

Recent systematic evidence-based efficacy reviews (Table 2) and published guidelines from the International Task Force on Canine AD provide recommendations for, and new approaches to, therapeutic interventions, based on whether the patient is experiencing an acute flare or has chronic skin lesions.

Approach to Acute Flares
Acute flares usually occur when allergens to which the dogs are sensitized are most prevalent. These flare factors include environmental (eg, house dust mites, pollens), food, and/or flea allergens, and can be exacerbated by secondary infections. Make an effort to identify, avoid, and/or eliminate these triggering and contributing factors.

When identifying flare factors:

- Look for evidence of fleas or flea dirt, especially in endemic areas
- Investigate possible ingestion of diet triggers to which the dog is known to be sensitive
- Investigate possible aeroallergen prevalence and exposure (eg, consultation of pollen count)
- Perform cytology (+/- bacterial skin culture and susceptibility, if indicated) to confirm the presence of bacterial and/or yeast skin and ear infections. These flares can be addressed with a combination of:
  - Frequent baths with mild, nonirritating antipruritic and/or antimicrobial shampoos and moisturizers
  - Short course of oral and/or topical glucocorticoids
  - Control of exposure to fleas and food allergens.
Approach to Chronic Disease

Similar to the approach to acute flares, triggering factors of chronic disease need to be identified and corrected. Focus management of chronic signs on identifying the safest and most efficacious long-term therapeutic modalities and managing chronic recurrent secondary infections, which can be done with a combination of interventions, including:

- Frequent baths with mild, nonirritating antipruritic and/or antimicrobial shampoos and moisturizers
- Anti-inflammatory and antipruritic systemic medications
- Allergen-specific immunotherapy (ASIT).

THERAPEUTIC MANAGEMENT:

Anti-Inflammatory & Antipruritic Medications

(Table 3, page 99)

**Topical Glucocorticoids**

This form of therapy is best suited for short-term use, particularly in acute flares, once to twice daily, to prevent potential adverse effects, such as cutaneous atrophy and calcinosis cutis.\(^2,9,10\)

There is fair evidence of efficacy of 0.015% triamcinolone acetonide and hydrocortisone aceponate spray for the treatment of CAD.\(^9-11\) Other topical glucocorticoids commonly used include betamethasone valerate and mometasone furoate cream.

**Oral Glucocorticoids**

Good evidence exists that demonstrates high efficacy of oral glucocorticoids for treatment of CAD.\(^9,10\)
• They are fast acting and, for many years, have been the mainstay treatment of CAD, particularly during acute flares.
• They are a less ideal treatment option for long-term management of chronic disease due to their broad, nonspecific anti-inflammatory response and many potential adverse effects.
• It is important to recognize, though, that some atopic dogs may require long-term glucocorticoids when other therapies fail, induce adverse effects, or cannot be attempted due to client financial limitations. If long-term systemic glucocorticoids are required, it is crucial to attempt identification of the safest and lowest dose and frequency that remains efficacious (e.g., a target dose for prednisone is 0.25–0.5 mg/kg PO Q 48 H). Injectable formulations should be avoided to minimize adrenal suppression.2,9-11

Ciclosporin
Good evidence exists that demonstrates high efficacy of ciclosporin, a calcineurin inhibitor, for treatment of CAD. Oral ciclosporin is approved for long-term management of CAD at 5 mg/kg PO Q 24 H, and adverse effects are uncommon at this dose. Ciclosporin can require 4 to 6 weeks to achieve satisfactory clinical improvement; therefore, it is not suitable for treatment of acute flares.2,9-11

Tacrolimus 0.1% Cream
Tacrolimus, another calcineurin inhibitor, has good evidence of efficacy.9-10 It is best suited for localized lesions and appears to be safe for short-term use.2,9-11

Misoprostol
Misoprostol, a prostaglandin E1 analogue, has good evidence of modest efficacy at 5 mcg/kg PO Q 8 H.9,10,12

Pentoxifylline
Pentoxifylline, a phosphodiesterase inhibitor, has fair evidence of efficacy at 10 mg/kg PO Q 12 H.2,9-11 However, a more recent study using higher doses—20 mg/kg PO Q 8 H—in combination with oral essential fatty acids (EFAs) showed more benefit.13

Pentoxifylline has a good safety profile but is not suited for acute flares due to its slow onset of action (4–6 weeks). It may be best suited as adjunctive therapy with medications, such as glucocorticoids, in chronic conditions.2,9

Recombinant Interferons
This form of therapy has some reported efficacy, however, dosage and protocols for optimal benefit and safety are currently unknown.9,11

Antihistamines & EFAs
Despite their extensive use in practice, there is insufficient evidence for or against the use of antihistamines and EFAs for treatment of CAD.2,9-11 While antihistamines and EFAs are not suited for acute flares, they may have some efficacy:2,9,10

• In patients with mild pruritus
• As part of combination therapy
• In a preventive role
• As sparing agents for glucocorticoids.

Oral antihistamines that may be used include:
• Fexofenadine (18 mg/kg PO Q 24 H)14
• Hydroxyzine (2 mg/kg PO Q 12 H)11
• Combination of hydroxyzine (20.9 mg/10 kg) and chlorpheniramine (0.7 mg/10 kg) (divided) PO Q 12 H15
• Cetirizine (0.5–1 mg/kg PO Q 12 H).11

There is no current evidence of superior efficacy of any EFA combination, dosage, ratio, or formulation, including enriched diets, to improve skin and coat quality and reduce pruritus in dogs with AD.2,9,10 I recommend high-quality fish oil with omega-3 EFAs—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—at 300 mg (180 mg of EPA and 120 mg of DHA) per 4.5 kg (10 lb) per day PO.11

Oclacitinib Maleate
Oclacitinib maleate, a JK inhibitor, is a new and unique oral targeted therapy that selectively inhibits JAK-1-dependent cytokines involved in allergic inflammation and pruritus, particularly IL-31.4 It is approved for treatment of allergic dermatitis or atopic dermatitis in dogs older than 12 months of age.

Studies. Several controlled studies have indicated an efficacy rate comparable to glucocorticoids and ciclosporin, with a fast onset of action (within 24 H) for control of pruritus.16-18 It is suitable for the treatment of acute flares as well as long-term management.17,19

Drug interactions. The safety of oclacitinib in combination with systemic immunosuppressive agents, such as glucocorticoids or ciclosporin, is unknown. It can be used safely with other common medications, such as antibiotics, nonsteroidal anti-inflammatory drugs, parasiticides, vaccinations, and allergy shots.
### TABLE 3.
**Selected Canine Atopic Dermatitis Therapeutic Agents**

<table>
<thead>
<tr>
<th>ACTIVE INGREDIENT</th>
<th>BRAND NAME</th>
<th>DOSAGE</th>
<th>KEY POINTS</th>
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<tbody>
<tr>
<td><strong>TOPICAL GLUCOCORTICOIDS</strong></td>
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</table>
| 0.015% Triamcinolone acetonide         | Genesis spray (virbacvet.com)  | Topically Q 12–24 H           | • Indicated for acute flares and localized lesions  
• Best suited for short-term use (7–14 days)  
• Adverse effects include cutaneous atrophy and calcinosis cutis |
| Hydrocortisone aceponate               | Cortavance spray (virbac.ca)   | Topically Q 12–24 H           |                                                                                                                                            |
| Betamethasone valerate                 | Otomax (merck-animal-health-usa.com) | Topically Q 12–24 H         |                                                                                                                                            |
| Mometasone furoate                     | Mometamax (merck-animal-health-usa.com) | Topically Q 12–24 H       |                                                                                                                                            |
| **ORAL GLUCOCORTICOIDS**               |                                |                               |                                                                                                                                            |
| Prednisone or prednisolone             | Generic formulations           | Induction or initial dose: 0.5–1 mg/kg PO Q 24 H and taper  
Target dose: 0.25–0.5 mg/kg PO Q 48 H | • Indicated for acute flares  
• Fast acting  
• Broad, nonspecific anti-inflammatory response  
• Many potential adverse effects |
| **CALCINEURIN INHIBITORS**             |                                |                               |                                                                                                                                            |
| Ciclosporin                            | Atopica (us.atopica.com)       | 5 mg/kg PO Q 24 H Initial dose: Can be tapered to the lowest dose that controls the disease | • Indicated for long-term management  
• Can take 4–6 weeks to achieve clinical improvement  
• Not suitable for treatment of acute flares  
• Most common adverse effects are gastrointestinal signs |
| Tacrolimus 0.1% cream                  | Protopic (protopic.com)        | Apply topically Q 12–24 H    | • Indicated for localized lesions  
• Appears to be safe for short-term use |
| **PROSTAGLANDIN E1 ANALogue**          |                                |                               |                                                                                                                                            |
| Misoprostol                            | Cytotec (pfizer.com)           | 5 mcg/kg PO Q 8 H            | • Modest efficacy |
| **PHOSPHODIESTERASE INHIBITOR**        |                                |                               |                                                                                                                                            |
| Pentoxifylline                         | Trental (products.sanofi.us)   | 10 mg/kg PO Q 12 H or 20 mg/kg PO Q 8 H | • May be best suited as adjunctive therapy for chronic conditions  
• Slow onset of action (4–6 weeks)  
• Not suitable for acute flares  
• Good safety profile |
| **ANTIHISTAMINES**                     |                                |                               |                                                                                                                                            |
| Fexofenadine                           | Allegra (allegra.com)          | 18 mg/kg PO Q 24 H           | • Helpful for mild pruritus  
• Best as part of combination therapy  
• Preventive role  
• Sparing agents for glucocorticoids  
• Not suitable for acute flares |
| Hydroxyzine                            | Generic formulations           | 2 mg/kg PO Q 12 H            |                                                                                                                                            |
| Hydroxyzine + chlorpheniramine         | Histacalmine (virbac.com)      | (20.9 mg + 0.7 mg)/10 kg (divided) PO Q 12 H |                                                                                                                                            |
| Cetirizine                             | Zyrtec (zyrtec.com)            | 0.5–1 mg/kg PO Q 12 H        |                                                                                                                                            |
| **ESSENTIAL FATTY ACIDS**              |                                |                               |                                                                                                                                            |
| High-quality fish oil (with EPA and DHA) | Generic formulations           | 300 mg/4.5 kg (10 lb) PO Q 24 H | • No current evidence of superior efficacy of any EFA combination, dosage, ratio, or formulation, to improve skin and coat quality and reduce pruritus |
| **JANUS KINASE INHIBITOR**             |                                |                               |                                                                                                                                            |
| Occlacitinib maleate                   | Apoquel (zoetisus.com)         | 0.4–0.6 mg/kg PO Q 12 H for 2 weeks; then Q 24 H | • Indicated for acute flares and long-term management  
• Fast onset of action (within 24 H) for pruritus control  
• Most common adverse effects are gastrointestinal signs  
• Contraindicated in dogs with serious infections or neoplasia  
• May increase susceptibility to infections, demodicosis, and neoplastic conditions |
| **IMMUNOTHERAPY**                      |                                |                               |                                                                                                                                            |
| Subcutaneous allergen-specific immunotherapy | Various protocols exist  
Adjust dosage and schedule for each patient |                                                                 | • Very specific targeted effect  
• Slow onset of action (up to 12 months)  
• Not useful for acute flares  
• Most common adverse reaction is worsening of pruritus |
| Sublingual immunotherapy               | Heska Allercept Therapy Drops (heska.com) | Pump dispenser directly onto oral mucosa, under and around the tongue, Q 12 H | • Most common adverse reactions are face rubbing, transient worsening of pruritus, and gastrointestinal signs |
**Effect on allergy testing.** It was shown to not interfere with allergy test results after 30 days of administration. More studies need to be conducted to demonstrate if longer use of Apoquel would affect the results of allergy testing.

**Contraindications & Adverse Effects.** Apoquel is contraindicated in dogs with serious infections and may increase susceptibility to infections, demodicosis, and neoplastic conditions. The most common adverse effects are gastrointestinal signs. Lethargy, unspecified benign cutaneous and subcutaneous masses, histiocytomas, papillomas, urinary tract infections/cystitis, pyoderma, and otitis have also been reported. Bone marrow suppression may be of concern, particularly if extra-label doses are used.

**Dosage & Monitoring.** The dose range recommended is 0.4 to 0.6 mg/kg PO Q 12 H, with or without food, for the first 2 weeks; then Q 24 H thereafter for maintenance.

Although the manufacturer of Apoquel does not recommend specific laboratory monitoring, I recommend frequent recheck visits to evaluate laboratory results, until more long term safety studies become available.

- **Baseline:** Complete blood cell count (CBC), serum biochemical profile, urinalysis (+/-) urine culture
- **1 month and 3 months post-treatment:** CBC
- **Every 6 months post-treatment:** CBC, serum biochemical profile, urinalysis, and urine culture

**THERAPEUTIC MANAGEMENT:**

**Antimicrobial Products**

**Antimicrobial Therapy**

If infection is not addressed, allergy management will fail completely. Due to the high incidence of multidrug resistance, minimize antibiotic use by favoring topical antimicrobials and narrow-spectrum antibiotics.

Milder and localized bacterial and yeast infections may be treated with topical antimicrobials, such as ointments, creams, gels, sprays, mousse, or wipes containing antiseptics, antibiotics, and/or antifungals.

More severe or generalized cases may require systemic antimicrobials. To identify and minimize antibiotic resistance in recurrent and unresponsive cases, choose the antibiotic based on culture and susceptibility testing. Proper duration and appropriate doses are important to minimize treatment failures and relapses and help prevent resistance.

New topical therapies include:
- Oxychlorine (Vetericyn spray, vetericyn.com)
- Chlorhexidine preparations (eg, Douxo Chlorhexidine + Climbazole mousse and spray, douxo.us)
- Baths with sodium hypochlorite (1–2 tablespoons of bleach per quart of water)

**Medicated Bathing**

Frequent soothing and/or antimicrobial, nonirritating shampoos and moisturizers may be helpful to minimize or control pruritus and infections in acute flares and chronic disease. However, no evidence currently exists that demonstrates any benefit from shampoos or conditioners containing lipids, oatmeal, pramoxine, antihistamines, or glucocorticoids.

Ten-minute, weekly baths with a shampoo containing antiseptics, lipids, and complex sugars (Allermyl, virbacvet.com) were shown to reduce pruritus within 24 hours in 25% of dogs.

**THERAPEUTIC MANAGEMENT:**

**Improving the Cutaneous Barrier**

Oral EFAs, nonirritating and moisturizing shampoos and sprays, and other topicals containing lipids, such as cholesterol, EFAs, and/or ceramide complexes, may be of benefit as adjunctive therapy to protect or improve the epidermal barrier.

Recent controlled studies suggest that ceramide-based topical products, such as Allerderm Spot-On (virbac.ca) and Dermoscent Essential-6 Spot-On (dermoscent.com), may help reduce clinical signs of AD in dogs.

**FIGURE 4. Use of sublingual immunotherapy, which is applied via a pump dispencer directly to the mucosa, under and around the tongue.**
A shampoo and spray that contains the ceramide precursor phytosphingosine (Douxocalm, douxo.us) and a shampoo containing antiseptics, fatty acids, and complex sugars (Allermyl, virbacvet.com) demonstrated similar clinical improvements.6

Further studies are needed to determine the true benefits of various therapies on cutaneous barrier impairment of atopic dogs.

**THERAPEUTIC MANAGEMENT:**

**Immunotherapy (Table 3, page 99)**

**Allergen-Specific Immunotherapy**

Attempt ASIT whenever CAD is diagnosed, as early as possible. ASIT remains the treatment of choice for long-term management of CAD due to its very specific targeted effect and safety, despite only a few controlled studies supporting its efficacy.2,6 It is not useful for acute flares due to its slow onset of action (up to 12 months).

Crucial aspects that maximize success and minimize adverse effects of treatment include:

- Careful selection of allergens correlating with environmental exposure
- Adjustment of dosage and schedule to suit the needs of each patient.

Subcutaneous ASIT has been administered for many years, with a 50% to 80% reported success rate.2,9-11

**Sublingual Immunotherapy**

Sublingual immunotherapy (SLIT), or “allergy drops,” is a recent form of allergen immunotherapy that is formulated with glycerin-based extracts in a vehicle that augments uptake through the oral mucosa and is typically customized for each patient based on positive reactions on allergy testing.

- The allergens are formulated and administered via a pump dispenser directly to the mucosa, under and around the tongue (Figure 4).
- These allergens are absorbed through the oral mucosa with uptake and processing by specialized oromucosal dendritic cells.

Although SLIT has been widely used in Europe for treating human allergies, it has only recently become available for treating animals in the United States.

**Advantages.** The main advantage of SLIT is ease of administration, which is beneficial for:

- Dogs that do not tolerate injections
- Owners who find injections difficult to administer or are frightened of needles.

The glycerin imparts a slightly sweet taste that many dogs view as a treat.

**Dosage.** The typically recommended protocol includes an indefinite twice daily dosing schedule.

Currently, several SLIT suppliers offer their own formulations with different protocols. A 1-year therapy trial is recommended, however, the ideal total duration of treatment is currently unknown.

**Safety & Adverse Effects.** SLIT appears to be very safe, and the most common adverse reactions are face rubbing, transient worsening of pruritus, and gastrointestinal signs that can resolve spontaneously within 1 to 2 weeks. If symptoms persist, the schedule may be altered to help manage side effects.

**Studies.** There are only a few studies demonstrating the efficacy of SLIT based on allergy testing for atopic dogs.25-28 An uncontrolled open clinical trial of SLIT for CAD, which used a formulation and dosing schedule equivalent to a commercial product (Heska Allercept Therapy Drops, heska.com), demonstrated an efficacy rate similar to injectable immunotherapy.25-28 Interestingly, 49% of dogs that previously had not responded to injection immunotherapy responded favorably to SLIT.

Future controlled trials are needed to determine the true efficacy of SLIT and demonstrate whether a particular formulation, dose, or administration schedule is superior for control of CAD.

**FUTURE THERAPEUTIC TARGETS**

Further studies are needed to investigate the potential benefits of other therapies for CAD, including other kinase inhibitors, monoclonal antibodies, diets, and nutraceuticals, such as probiotics. Advances in our understanding of this complex and fascinating disease will continue to contribute to new therapeutic solutions in the future.

**The Importance of Flea Control**

Evidence exists that atopic dogs are predisposed to hypersensitivity reactions when exposed to flea salivary antigens. Therefore, all dogs with AD should receive year-round flea preventives. Identify flea infestations and flea-allergy dermatitis and consider them potential triggering factors of allergy flares.2,9

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AD = atopic dermatitis; ASIT = allergen-specific immunotherapy; CAD = canine atopic dermatitis; CBC = complete blood cell count; DHA = docosahexaenoic acid; EFA = essential fatty acid; EPA = eicosapentaenoic acid; IgE = immunoglobulin E; JK = Janus kinase; SLIT = sublingual immunotherapy

References