

 **WSAVA**
Global Veterinary Community

Canine Atopic Dermatitis

Jeanne B. Budgin, DVM
Diplomate American College of Veterinary Dermatology
Riverdale Veterinary Dermatology
Riverdale, New Jersey USA

  wsva.org

Canine Atopic Dermatitis (CAD)

- Genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features
- Associated with immunoglobulin E (IgE) antibodies most commonly directed against environmental allergens

CAD

- 2-15% of the canine population
- Typical age of onset: 6 months to 7 years (70% between 1 and 3 years)
- Breed predispositions
- No pathognomonic signs
- Localized vs. generalized
- Significant overlap with other pruritic diseases



CAD: What We Used to Think

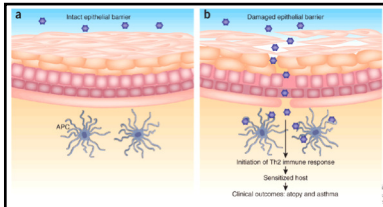
IgE-mediated disease like human hay-fever

Inhaled Allergen
↓
Mast Cell Degranulation
↓
Itchy Skin

What We Used to Think

What We Think We Know Now

- Outside Inside Hypothesis
 - Defects in the barrier function of the skin lead to penetration of allergens that initiate immune response



What We Think We Know Now

Genetic and Environmental Factors
 ↓
 Epidermal Barrier Dysfunction
 Increased Transepidermal Water Loss
 ↓
 Deeper Penetration by Allergens
 Colonization by Bacteria and Yeast
 ↓
 Aberrant Immune Response

Epidermal Barrier Dysfunction

- Genetic Factors
 - Mutation in Filaggrin (key protein)
 - Deficiency of Ceramides (key lipids)
 - Abnormal desquamation (key event)
 - Structural abnormalities in and between cells
- Environmental Factors
 - House dust mite proteases
 - Staphylococcal exfoliative exotoxins

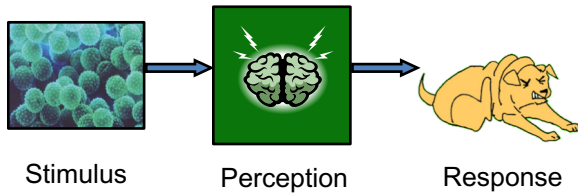
Clinical Signs of CAD

- Pruritus
 - Must be present
 - Should be present in absence of lesions
 - “itch that rashes” vs. “rash that itches”

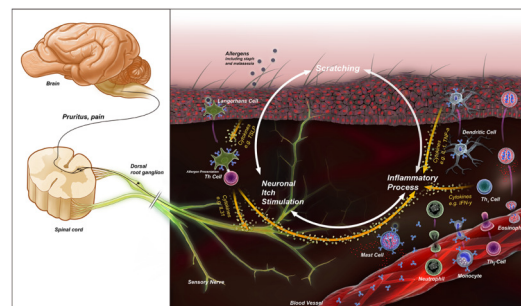


What Is Pruritus?

An unpleasant sensation provoking desire to scratch . . . or itch, bite, rub, lick, scoot, chew, roll or shake



Pruritus Is Complex



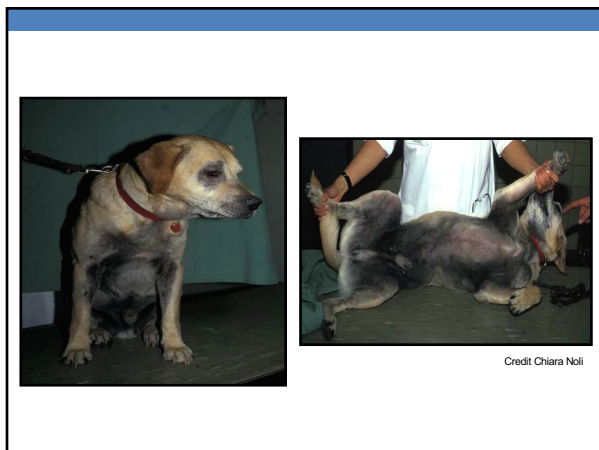
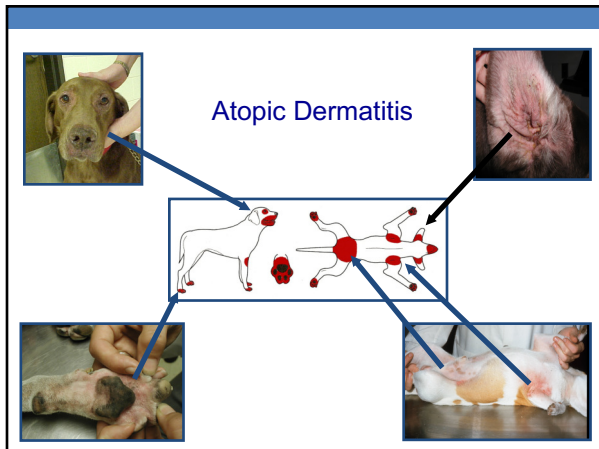
Courtesy: Zoetis Animal Health www.ItchCycle.com

Important Cytokine IL-31

- IL-31
 - Produced by Th2 lymphocytes
 - High levels in many allergic dogs
 - Direct stimulation of peripheral nerves
- Itch cytokine - few other functions known
- If non-atopic dogs injected with IL-31 → they start itching
- If IL-31 is blocked → they stop itching

Clinical Signs

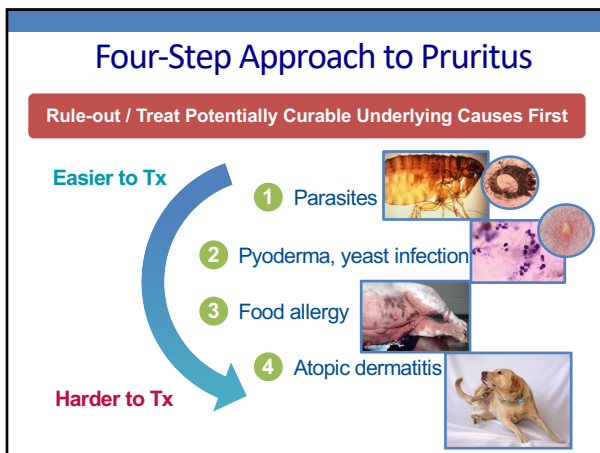
- Most commonly affected areas
 - Pinnae (58%)
 - Axillae (62%)
 - Abdomen (66%)
 - Front feet (79%)
 - Hind feet (75%)
 - Lips (42%)
 - Perianal (43%)



Diagnostic Approach - History

- Duration of pruritus
 - Often long duration for allergies (months to years)
 - Short time for infectious, parasitic and some neoplastic diseases (days to weeks)
- Seasonality
 - Flea allergy dermatitis
 - Atopic dermatitis





- ## Differential Diagnoses
- Other hypersensitivity
 - FAD, CAFR, contact allergy
 - Ectoparasites
 - Fleas, *Sarcoptes*, *Cheyletiella*, *Demodex*, *Otodectes*
 - Infectious
 - Staphylococcal or *Malassezia* dermatitis, dermatophytosis
 - Neoplasia
 - Cutaneous lymphoma
 - Immune-mediated disease
 - Pemphigus foliaceus, cutaneous drug reaction

Hensel et al. BMC Veterinary Research (2015) 11:196
DOI 10.1186/s12917-015-0515-5

BMC Veterinary Research
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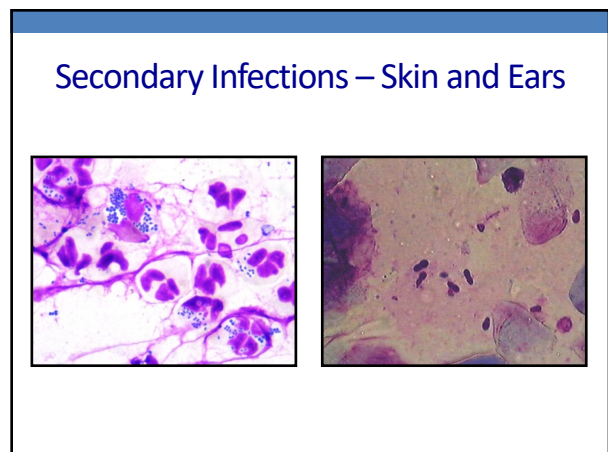
Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification

Patrick Hensel^{1*}, Domenico Santoro^{2†}, Claude Favrot³, Peter Hill⁴ and Craig Griffin^{5†}

Abstract
Background: Canine atopic dermatitis (AD) is a common, genetically predisposed, inflammatory and pruritic skin disease. The variation in clinical presentations, due to genetic factors, extent of the lesions, stage of the disease, secondary infections, as well as resemblance to other non-atopic related skin diseases, can complicate a diagnosis of canine AD. A sub-group of the International Committee for Allergic Diseases in Animals (ICADA) was tasked with the development of a set of practical guidelines that can be used to assist practitioners and researchers in the diagnosis of canine AD. Online citation databases and abstracts from international meetings were searched for publications related to the topic, and combined with expert opinion where necessary. The final set of guidelines was approved by the entire ICADA committee.
Results: A total of 81 publications relevant for this review were identified. The guidelines generated focus on three aspects of the diagnostic approach:
 1. Ruling out of other skin conditions with clinical signs resembling, or overlapping with canine AD.
 2. Detailed interpretation of the historical and clinical features of patients affected by canine AD.
 3. Allergy testing by intradermal versus allergen-specific IgE serum testing.
Conclusions: The diagnosis of canine AD is based on meeting clinical criteria and ruling out other possible causes with similar clinical signs. Flea combing, skin scraping and cytology should be performed, where necessary, as part of a thorough work-up. Elimination diet trials are required for patients with perennial pruritus and/or concurrent gastrointestinal signs. Once a clinical diagnosis of canine AD is made, allergy testing can be performed to identify potential causative allergens for allergen-specific immunotherapy.

- ## Management Goals for CAD
- Manage secondary infections
 - Address defective epidermal barrier
 - Address immunological imbalance
 - Allergen specific immunotherapy (ASIT)
 - Keep pet comfortable
 - Antihistamines and EFAS
 - Glucocorticoids
 - Cyclosporine (Atopica®, Elanco)
 - Oclacitinib (Apoquel®, Zoetis)
 - Lokivetmab (Cytopoint®, Zoetis)
- 

- ## Manage Secondary Infections
- Skin and ear infections are VERY common
 - May add significantly to overall pruritus
 - Treating infections alone can significantly reduce pruritus
 - Different presentations for different breeds
 - Perform cytology
 - Culture when indicated



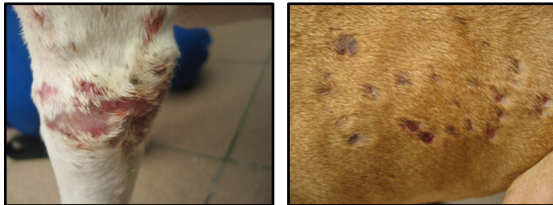
Bacterial Folliculitis



Superficial Spreading Pyoderma



Deep Pyoderma



Systemic Antibiotic Principles

- Always combine with topical therapy
- Duration of treatment
 - 1-2 weeks beyond clinical cure
 - Re-evaluate patient prior to completing antibiotic therapy
- Safety – minimize risk to patient
- Efficacy
 - Culture and sensitivity
 - High end of dose ranges

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Topical Therapies



Benefits of Bathing for CAD

- (1) Remove irritants/debris
- (2) Remove allergens
- (3) Decrease pruritus
- (4) Reduce bacteria/yeast
- (5) Restore epidermal barrier function



"The more we do on the outside, the fewer drugs we need on the inside"

Shampoo Protocol

- Usually performed twice weekly but may be more often based on severity of condition
- Maintenance is every 7-10 days
- Cool to luke warm water
- 10 min contact time minimum
- Air dry



Antipruritic Agents

- Soothing/antipruritic ingredients
 - Water!
 - Emollients and moisturizers (fatty acids, ceramides, PS)
 - Colloidal oatmeal
 - Antihistamines
 - Anesthetics
 - Glucocorticoids



Ceramides

- Fatty acids linked to a sphingoid base
- Topical use (canine)
 - Reduced transepidermal water loss
 - Improved hydration
 - Reduced lesion and pruritus scores
 - Intercellular lipids became normal and organized

Jung et al. Clinical use of a ceramide-based moisturizer for treating dogs with atopic dermatitis. *J Vet Sci.* June 2013.



Phytosphingosine

- Sphingolipid, proceramide
- Antibacterial
- Antifungal
- Anti-pruritic
- ↓ transepidermal water loss



Spot-on Products

- Repair and restores the skin barrier function
- Dermoscent® Essential 6 (Bayer)
 - Essential fatty acids, vitamin E, and a blend of oils
- Douxo Seborrhea Spot On® (CEVA)
 - Phytosphingosine



Colloidal Oatmeal and Antihistamines

- Exact mechanism of action of oatmeal unknown
- Contact dermatitis has been reported
- Few studies show any efficacy
- Douxo Calm
 - Avenanthramides + PS
 - Most active portion of colloidal oatmeal



Pramoxine

- Pramocaine
- Anti-pruritic and soothing
- Topical anesthetic → blocks sodium channels and nerve impulses
- Efficacy (Scott et al. 2000)
 - Good reduction in pruritus in 41% of dogs lasting 48 hours



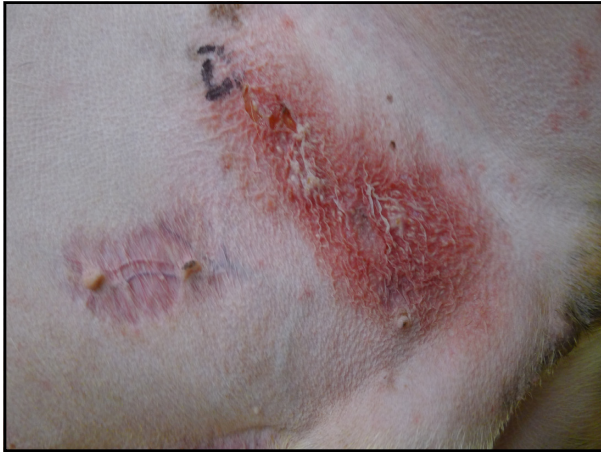
Glucocorticoids

- Useful for localized pruritus
- Limited time frame to avoid adrenal suppression
- Relative strength of products



Glucocorticoids

- Avoid more potent topical preparations for long-term use
 - Epidermal atrophy and skin fragility
 - Comedones
 - Localized demodicosis
- Systemic absorption or ingestion from licking products



Antimicrobial Agents

- Antibacterial
 - Chlorhexidine
 - Benzoyl Peroxide
 - Ethyl Lactate
 - Chloroxylenol
- Antifungal
 - Miconazole
 - Ketoconazole
 - Chlorhexidine (3%)
 - Climbazole



Antimicrobial Action

- Study comparing the efficacy of shampoos
- Antimicrobial efficacy is “highly variable”
- Only the chlorhexidine products had consistent broad spectrum activity
- Chloroxylenol and acetic acid/boric acid shampoos had little to no antibacterial activity; some anti-Malassezia activity
- Ethyl lactate shampoo not effective

Young et al. Comparative in vitro efficacy of antimicrobial shampoos: a pilot study. *Vet Dermatol* 2012.

Chlorhexidine

- Works well in organic debris and has residual effect of 48 hours
- Ten minute contact time important!
- Antimicrobial activity is superior to povidone iodine and ethyl lactate; less drying than benzoyl peroxide
- 3-4% concentration or 2% combined with miconazole effective for Malassezia
- Available in shampoo, sprays, wipes and mousse

Other Topical Formulations

- Spray/mousse
 - Used as adjunct treatment with shampoos
- Advantages
 - Use without entire bathing process
 - Use in between baths
 - Enforce antimicrobial/barrier function of shampoos



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Immunotherapy (ASIT)

- Therapies to keep patients comfortable are not a substitute for a complete allergy work-up
- ASIT is still most recommended therapy for long term control
 - Modulates T-cell ratios → decreased response when exposed to allergens
 - In humans, slows progression of disease
- Subcutaneous injection or sublingual drop



Allergen-specific Immunotherapy

- Response rates (multiple studies)
 - Excellent : 20-38%
 - Partial: 60-100%
 - Failure: About 20%
- 4-12 months for benefit of ASIT
- Goal is improved quality of life and less dependence on systemic medications

Why an Intradermal Skin Test (IDST)?

- Tests the target organ
- Tests for functional “pathogenic” IgE
 - IgE on the surface of mast cells capable of causing degranulation (“wheal”) and affecting dermal microvasculature
- May evaluate for delayed reactions
- Fewer irrelevant cross reacting allergens (↓ false positive reactions)
- Only test that can reliably diagnose *Malassezia* hypersensitivity
- Results and immunotherapy available the same day

Allergen-specific IgE serology

- Advantages
 - No sedation or shaving required
 - Quantitative results
 - Readily available to all veterinarians
 - Less influenced by concurrent drug therapy
 - No experience required to perform and interpret the test

Allergen-specific IgE serology

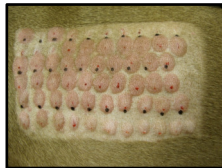
- Disadvantages
 - Results are not reproducible
 - Low specificity (↑ false positive reactions)
 - Cut offs between negative and positive results are arbitrary
 - Presence and quantity of allergen specific serum IgE does not correlate with the severity of clinical signs
 - Methodology, standardization and quality control varies by laboratory with few critical studies evaluating performance

Allergy Serology Test Considerations

- Scientific basis of the assay
- Published results of studies using the assay
- Laboratory’s involvement in allergy research
- Quality and efficiency of the service
- Availability of qualified staff for consultation
- Cost

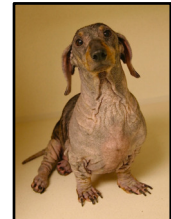
IDST vs. Serology

- Ideally both tests should be performed
- ASIT based on combined results of both tests had superior correlation (93%) with the history and clinical signs in dogs with seasonal atopic dermatitis



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Antihistamines

- Little evidence for efficacy in CAD
- Anecdotally many practitioners and clients report some success
- May be helpful for acute allergy flares or very mild pruritus
- Cetirizine and hydroxyzine

Antihistamines

- Limitations
 - Histamine plays a small role
 - Low efficacy compared to other therapies
- Uses?
 - CAD only
 - May be synergistic with other therapies
 - EFAs
 - Prednisolone (Temaril P®)
 - Few side effects or contraindications

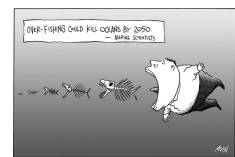


Essential Fatty Acids (EFAs)

- Omega 6 → barrier function
- Omega 3 → anti-inflammatory/pruritic effects
- 180 mg EPA and 120 DHA per 10 lbs BW
- Require 4-6 weeks for initial benefit; 8-12 weeks for full benefit
- One study decrease in prednisolone requirement by ~50%
- Adverse effects – 5% GI signs
- Use fish > flax sources for omega 3

EFA Considerations

- Salmon is over-fished world wide and quality of fish-farming is variable
- Consider smaller non-predatory, renewable high fat species (anchovies, sardines)
- Lack of standardization and poor quality control



EFA Considerations

- Important to test for heavy metals, ocean pollutants, contamination
- EPA/DHA content listed in mg on label
- Form of fish oil is important!
 - Triglycerides most common with relatively low levels of EPA/DHA
 - Free form is best

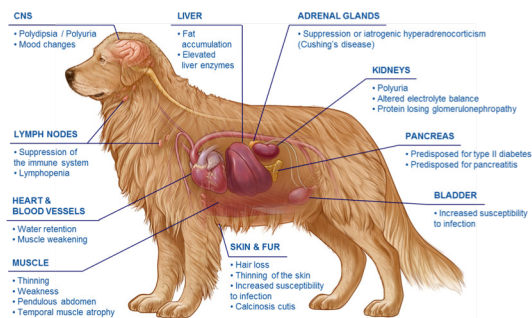


Glucocorticoids

- Partial to excellent response in 75-97% of atopic dogs
- Many side effects
- Try to avoid long term use – use for temporary relief of intense itch or for acute and chronic otitis externa



Canine Organs Affected by Glucocorticoids



Glucocorticoid Options

- Long acting injectables
 - Contain molecules that alter solubility
 - Slow release from tissue/prolonged absorption
 - Continuous release → more side effects
 - Can not adjust dose once given
- Oral always recommended over injectable therapy



Glucocorticoid Options

- Medrol® (Zoetis) vs. prednisone
 - Less mineralocorticoid effects → less polyuria/polydipsia
 - Same dose and tapering protocol
- Other oral formulations
 - Triamcinolone, dexamethasone
 - Will rarely use for refractory cases
 - Will taper to q 72 hour dosing
- Steroid equivalence converter: medcalc.com/steroid.html



Cyclosporine (Atopica®)

- Inhibits interleukin-2 (IL-2)
- Suppresses T-helper and T-suppressor lymphocytes
- Efficacy equivalent to prednisolone in many studies
- Not for acute pruritus due to slow onset of action (3-4 weeks)
- May often taper to q 48 – 72 hours after 4-6 weeks
- Generic modified formulation often as effective



Cyclosporine (Atopica®)

- Side effects
 - Vomiting 30%
 - Diarrhea 20%
 - Gingival hyperplasia 2.3%
 - Excessive shedding <2%
 - Papilloma-like lesions
 - Increased hair growth
- Contraindicated in animals with a history of neoplasia



Oliver et al. BMC Veterinary Research (2015) 11:210
DOI 10.1186/s12917-015-0144-4



CORRESPONDENCE

Open Access

Treatment of canine atopic dermatitis: 2015 updated guidelines from the International Committee on Allergic Diseases of Animals (ICADA)

Thierry Olivry^{1*}, Douglas J. DeBoer², Claude Favrot³, Hilary A. Jackson⁴, Ralf S. Mueller⁵, Tim Nuttall⁶, Pascal Pétiaud⁷ and for the International Committee on Allergic Diseases of Animals

Abstract
Background: In 2010, the International Task Force on Canine Atopic Dermatitis (now International Committee on Allergic Diseases of Animals, ICADA) published the first consensus guidelines for the treatment of atopic dermatitis (AD) in dogs. This is the first 5-year minor update of this document.
Results: The treatment of acute flares of AD should involve the search for, and then elimination of, the cause of the flares, bathing with mild shampoos, and controlling pruritus and skin lesions with interventions that include topical and/or oral glucocorticoids or oclacitinib. For chronic canine AD, the first steps in management are the identification and avoidance of flare factors, as well as ensuring that there is adequate skin and coat hygiene and care; this might include more frequent bathing and possibly increasing essential fatty acid intake. The medications currently most effective in reducing chronic pruritus and skin lesions are topical and oral glucocorticoids, oral oclacitinib, oral oclacitinib, and, where available, injectable recombinant interferons. Allergen-specific immunotherapy and proactive intermittent topical glucocorticoid applications are the only interventions likely to prevent or delay the recurrence of flares of AD.
Conclusions: This first 5-year minor update of the international consensus guidelines for treatment of AD in dogs further establishes that the treatment of this disease is multifaceted and that interventions should be combined for a proven (or likely) optimal benefit. Importantly, treatment plans are likely to vary between dogs and, for the same dog, between times when the disease is at different stages.
Keywords: Atopic dermatitis, Canine, Dogs, Evidence-based medicine, Guidelines, Treatment

Back to IL-31

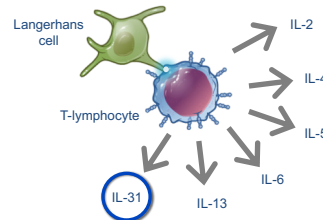
In the skin, cytokines regulate acute and chronic processes such as neuronal itch stimulation and inflammation.

Neuron in skin



Cytokines Involved in Canine Allergic Skin Disease

Cytokines Implicated in Allergic Skin Disease (e.g., Atopic Dermatitis) Are Secreted from Activated T-lymphocytes



- Activate other immune cells involved in allergy and inflammation
- Continued breakdown of skin barrier
- Induction of neuronal itch stimulation

McCandless et al. Vet Immunol Immunopathol. 2014 Jan;157(1-2):42-48.c

Oclacitinib Mechanism of Action

- Inhibits Janus kinase (JAK) enzymes
 - JAK1 and JAK3
 - Inhibits pro-inflammatory and pro-allergic cytokines that use JAK1 (Th2)
- Minimal impact on cytokines from JAK2
 - Hematopoiesis and innate immunity (Th1)

Oclacitinib

- Indications
 - Acute or chronic pruritus in canine allergic dermatitis
 - > 12 months of age
- Dosing
 - 0.4–0.6 mg/kg PO q 12 hrs x 14 days, then q 24 hours maintenance
 - Some need their total daily dose divided twice a day (off label)
 - May be used with many other common drugs, vaccines and ASIT
 - Not evaluated with glucocorticoids
 - May use concurrently with cyclosporine for 3 weeks

When Not To Use Oclacitinib

- Dog is well controlled on another treatment that has high safety profile
 - Antihistamines, EFAs, topicals
 - Cyclosporine
 - ASIT
- Recent history of demodicosis
- Deep infection
- Neoplasia
- Pregnant, lactating or breeding animals

My Experiences with Apoquel®

- Works very well but not in all patients
- Minimal side effects with no increased risk of neoplasia
- Best to try and lower daily dose vs. administer every 48 hours
- Best to not exceed 0.6 mg/kg PO q every 24 hours or give q 12 hours > 14 days
- Does not work well for otitis externa, anal sacculitis, sarcoptic mange (without concurrent parasiticides) or with concurrent deep infection
- Monitoring (no specific FDA recommendations)
 - Baseline CBC/Chem then at 1 month, then every 6 months

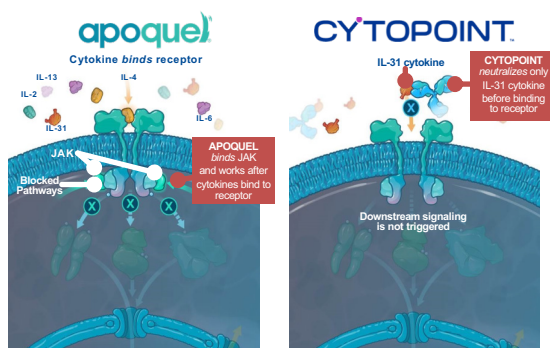
New Therapy - Lokivetmab

- Cytopoint®
- Monoclonal antibody against IL-31
- One injection every 4-8 weeks



Apoquel® vs. Cytopoint®

- Both block IL-31
 - Major itch cytokine
 - No other functions known
- Work in different ways
 - Apoquel® - blocks Janus kinase receptor
 - Cytopoint® - mAb against IL-31
- Very effective for acute pruritus
- Long term safety studies needed



My Ideal Strategy for CAD

- Year round effective parasite control (isoxazolines)
- Topical therapies to address barrier function and infection (Douxo® Chlorhexidine PS shampoo +/- weekly Dermoscent® spot-on)
- EFA supplementation (Free Form™ snip tips) or Royal Canin® Skin Support diet
- ASIT for long term control with use of Apoquel® or Cytopoint® as needed during induction or for allergic flares

CAD - Key Points

- CAD is a diagnosis of exclusion with signalment, history, clinical signs and response to therapy all aiding in the diagnosis
- Remember your basic derm diagnostics!
- Important to control parasites and manage secondary infections
- Topical therapies are of tremendous benefit to reduce infection and improve barrier function
- Apoquel® and Cytopoint® are exciting, safe and effective therapies to control symptoms
- Consider referral and immunotherapy for long term management