CANINE PRURITUS: DIAGNOSTIC APPROACH & TREATMENT UPDATES

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Lecture Agenda
- Review a case for a practical approach to the pruritic dog
- Pathophysiology of atopic dermatitis
- Clinical signs and diagnostic approach
- Management
- Conclusions

Case Presentation
Signalment: "Mr. Fudge" Canine, West Highland white terrier, male neutered, 6 years old

Dermatological History
- Age of onset
- Familial history
- Type, localization, distribution, and evolution of the lesions
- Location and severity of pruritus (VAS)
- Seasonality
- Response to previous treatments
- Other pets/humans affected
- History of gastrointestinal signs

Mr. Fudge's History
- 4-year history of non-seasonal pruritic skin disease
- Previous food trial with OTC venison and duck-based diets for 6 weeks
- Previous improvement with oral antibiotics and prednisone therapy
- No other pets or humans affected
- Chronic semi-formed stool (4-5 bowel movements/day)
- VAS: 9/10

Differential Diagnoses
- Ectoparasites (fleas, scabies, demodex)
- Allergic skin disease - atopic dermatitis, adverse food reaction (AFR) flea allergy dermatitis
- Infectious - superficial pyoderma, Malassezia dermatitis, dermatophytosis

Diagnostic Tests
- Flea combing → negative
- Superficial and deep skin scraping → negative
- Skin cytology: impression smear beneath crusts → add on aerobic culture: methicillin resistant *Staph pseudintermedius*
- Skin cytology: acetate tape preparation
- CBC/Chemistry/thyroid panel/U/A → mild neutrophilia and monocytosis; mild hyperglobulinemia
- U/A: 2+ proteinuria; UPC < 0.30 (normal < 0.50)
- Fecal O/P and Giardia → negative

Treatment Plan - Mr. Fudge's Re-examination (4 wk)
- Body weight was stable and the Ultamino diet had been fed exclusively for four weeks

- Compliance was excellent
- Stool consistency and frequency of defecation (3x/day) were improved
- Repeat cytology revealed resolution of infection
- Pruritus score 6/10 vs. 9/10 (VAS)

Why Still So Pruritic?
- Additional time required on food trial for improvement
- Other concurrent allergy (atopic dermatitis)
- Ectoparasitism (unlikely)
- Persistent infection (not supported clinically or cytologically)

Revised Treatment Plan
- Begin Apoquel® PO q 12 hours x 14 days, then q 24 hours x 14 days
- Continue shampoo therapy, probiotics, monthly selamectin, and Ultamino dietary trial
- Re-examination in six weeks

Mr. Fudge's Re-examination (10 wk)
- Body weight was stable and the Ultamino diet had been fed exclusively for ten weeks
- Compliance was still excellent
- Pruritus was improved – 2/10 (VAS) on Apoquel but increased to 4/10 after discontinuing
- Scheduled for intradermal skin testing

Revised Treatment Plan
- Challenge back with previous diet with close observation over the next two weeks → flare with 9/10 (VAS)
- Owner elected to continue feeding Ultamino long term
- Begin immunotherapy (IT) injections
- Re-start Apoquel® and try to lower over time to determine if IT is beneficial
- Discontinue probiotics; continue shampoo therapy weekly and selamectin monthly

Mr. Fudge Take Home
- Remember basic diagnostics including evaluating for infections and parasites
- Perform an aerobic culture when bacterial infection persists or in patients with a history of exposure to multiple antibiotics
- Treat infections for a minimum of 30 days
- Continue food trial for a total of 8-10 weeks with monthly re-examinations
- If sustained improvement is documented, don't forget to re-challenge!

<u>Canine Atopic Dermatitis (CAD)</u>
- Genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features
- Associated with immunoglobulin E (IgE) antibodies most commonly directed against environmental allergens
- 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 in clinical signs with other pruritic diseases

<u>Pathophysiology</u>
What We Used to Think
- IgE-mediated disease like human hay-fever
- Inhaled allergen → mast cell degranulation → itchy skin

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
- Genetic and environmental factors → epidermal barrier dysfunction → increased transepidermal water loss → deeper penetration by allergens and 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
- Pruritus must be present and should be present in absence of lesions - "itch that rashes" vs. "rash that itches"
- Pruritus Is Complex – important cytokine 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

Most Commonly Affected Areas
- Pinnae (58%)
- Axillae (62%)
- Abdomen (66%)
- Front feet (79%)
- Hind feet (75%)
- Lips (42%)
- Perianal (43%)

Diagnostic Approach
- Signalment and History
- Four-Step Approach to Pruritus
- 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

Flea Allergy Dermatitis (FAD)
- Most common skin disease affecting dogs worldwide
- May be seasonal depending on climate
- No age predilection
- Typically will see evidence of fleas but not always
- May have fleas without FAD
- Few fleas can cause profound reaction
- Typically caudal half of body

FAD Diagnosis

- History and physical examination
- Presence of fleas or "flea dirt"
- Intradermal test – not commonly used
- Response to intensive flea control or prevention

FAD Management
- Flea control
- Control of pruritus
- Treatment of secondary infections
- Improvement usually seen within 7 to 14 days after elimination of the fleas

Newer Products - Isoxazolines
- Derived from sea sponge molecule
- Inhibit GABA gated Cl^- gated channels
- Highly effective against fleas/ticks with rapid knockdown
- Studies and experience confirm excellent efficacy against mites
  - Afoxolaner (Nexgard™, Merial)
  - Fluralaner (Bravecto®, Merck)
  - Lotilaner (Credelio™, Elanco)
  - Sarolaner (Simparica™, Zoetis)

<u>Sarcoptes scabiei</u>
- Primarily a problem in canids
- Burrow into the cornified layer of the epidermis and lay eggs
- Severe pruritus develops as an IgE-mediated reaction to intestinal proteins found in the fecal material
- Highly contagious

Scabies Diagnosis
- History and lesion distribution
- Pinnal pedal reflex
- Identification of mites, eggs or fecal pellets on a skin scraping; can be difficult
- Positive ELISA test (2 to 4 weeks after infestation)
- Response to therapy

Scabies Management
- Treat all in contact animals and environment if > 1 dog in the household or human with bites
- Isolate from other animals
- Isoxazolines (off label) at label doses
- Selamectin (Revolution®) q 2 weeks for 3 treatments
- Lime sulfur dips x 5-7 days
- Amitraz, ivermectin, fipronil (spray), moxidectin/imidocloprid (spot-on)
- Manage pruritus and secondary infections

<u>Management Goals for CAD</u>
- Manage secondary infections
- Address defective epidermal barrier
- Keep patient comfortable
  - Antihistamines and essential fatty acids (EFAs)
  - Glucocorticoids
  - Cyclosporine (Atopica®, Elanco; Cyclavance™, Virbac)
  - Oclacitinib (Apoquel®, Zoetis)
  - Lokivetmab (Cytopoint®, Zoetis)
- Address immunological imbalance - allergen specific immunotherapy (ASIT)

Manage Secondary Infections
- Skin and ear infections are VERY common and add significantly to overall pruritus
- Treating infections alone can significantly reduce pruritus

- Different presentations for different breeds
- Perform cytology
- Culture when indicated
    - Recurrent pyoderma
    - Pyoderma previously treated with multiple antibiotics
    - Pyoderma poorly responsive to empirical treatments
    - Deep pyoderma
    - Pyoderma with cytological evidence of rod bacteria

Systemic Antibiotic Principles
- Always combine with topical therapy
- Duration of treatment - 1 week beyond clinical cure and re-evaluate patient prior to completing antibiotic therapy
- Safety – minimize risk to patient
- Efficacy - culture and sensitivity; often high end of dose range

Topical Therapies

Shampoo – benefits
- Remove irritants/debris
- Remove allergens
- Remove bacteria/yeast
- Decrease pruritus
- Improve epidermal barrier function

Shampoo Protocol
- Usually performed twice weekly but may be more often based on severity of condition
- Maintenance is every 7-10 days
- Cool to lukewarm water
- 10 min contact time minimum
- Towel and air dry

Mousses and Foams
- Localized or full body treatment
- Often combined with or used as a replacement for bathing
- Longer residual effect vs. shampoo - ten days vs. *Staph pseudintermedius* in vitro
- Pleasant application experience through massage

Pads and Wipes - work well within folds and for feet
- Ingredients may be irritating – acetic acid, alcohol

Lotions/Creams/Ointments/Gels
- Best for localized lesions
- May need to remove fur for effective application
- Apply once to twice daily until resolution (14-21 days)
- Good residual effect but may be messy
- Deter licking for 20 minutes following - feed, walk, E collar, socks, or booties

Spot-Ons
- Localized or more generalized application
- Most effective if used after bathing
- Once-twice weekly

<u>Antimicrobial Agents - Antibacterial</u>
- Chlorhexidine
- Benzoyl Peroxide
- Ethyl Lactate
- Chloroxylenol
- Silver sulfadiazine
- Mupirocin

- Medical grade honey
- Sodium hypochlorite (bleach)

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

Chlorhexidine
- Broad spectrum – gram +/- bacteria - 3-4% concentration (fungistatic) or 2% combined with miconazole effective for Malassezia
- Bactericidal – disrupts cell membrane → impaired cellular exchange and precipitation of nucleic acid
- Works well in organic debris with residual effect of 48 hours
- Ten-minute contact time important!
- Available in many formulations

Silver Sulfadiazine
- Silver + sulfonamide
- Bactericidal and antifungal – very effective for *Pseudomonas* sp.
- Silver acts on cell membrane
- Inhibits protein synthesis
- Poor skin penetration

Mupirocin
- Inhibits protein and RNA synthesis
- Effective for Staphylococcal infections
- Effective against most strains of methicillin resistant *S. pseudintemedius* (MRSP)
- Penetrates tissue well

Medical Grade Honey
- Multiple antimicrobial compounds - methylglyoxal
- High osmolality
- Release of oxygen compounds
- Lower skin pH
- Manuka honey
    - Sourced from Manuka trees (*Leptospermum scoparium*)
    - High levels of antibacterial phytochemicals
    - Efficacy not affected by antibiotic resistance

Sodium Hypochlorite (dilute bleach)
- Bactericidal at high concentrations
- Inhibits cell wall formation
- Must be made fresh
- Very short acting

<u>Antifungal Agents - Azoles</u>
- Inhibit synthesis of ergosterol, a major component of fungal cell membrane
- Antibacterial properties including synergism with miconazole/chlorhexidine
- Well established efficacy with low level resistance
- Miconazole > ketoconazole, climbazole
- Chlorhexidine 3%+

<u>Antipruritic Agents</u>
- Water
- Colloidal oatmeal
- Antihistamines
- Anesthetics
- Glucocorticoids

- Calcineurin-inhibitors
- Ophytrium™

Colloidal Oatmeal and Antihistamines
- Exact mechanism of action of oatmeal unknown
- Contact dermatitis has been reported
- Few studies show any efficacy
- No data to support the efficacy of topical antihistamines

Topical Anesthetics
- Pramoxine
    - Anti-pruritic and soothing
    - Topical anesthetic → blocks sodium channels and nerve impulses
- Efficacy
    - Satisfactory reduction in pruritus in <20-30% of dogs with leave-on lotion
    - Estimated antipruritic effect of 48 hrs

Glucocorticoids - Useful for localized pruritus
- Classified by potency
    - Low – hydrocortisone
    - Intermediate - prednisolone, triamcinolone, dexamethasone
    - High - betamethasone, fluocinolone, mometasone
- Start with an intermediate or high potency corticosteroid
- Switch to a low potency one for long term use
- Avoid potent products long-term
    - Adrenal suppression
    - Epidermal atrophy and skin fragility
    - Comedones
    - Localized demodicosis
    - Systemic absorption or ingestion from licking products

Calcineurin Inhibitors - Protopic® (tacrolimus 0.1%)

Ophytrium™
- Purified natural extract from roots of *Ophiopogon japonicus* (dwarf lilyturf)
- Limits release of pro-inflammatory and Th2 cytokines
- Beneficial effect on all 3 skin barriers

<u>Barrier/Microbiota Restoration Agents</u>
- Outside-inside barrier
    - Prevents mechanical damage
    - Prevents penetration by external factors – microorganisms, allergens, chemicals/toxins, UV radiation
- Inside-outside barrier – prevents water loss
    - Prevents water loss

Ceramides and fatty Acids
- Restructure stratum corneum
- Control sebum production
- Control microbial flora
- Improve hydration

Sphingolipids + Glycosaminoglycans
- Atopivet™ line - Sphingomyelin + hyaluronic acid - shampoo, mousse, collar, and spot-on

Keep Patient Comfortable

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

- Limitations - histamine plays a small role in CAD + low efficacy compared to other therapies
- 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 of body weight
- Require 4-6 weeks for initial benefit; 8-12 weeks for full benefit
- Adverse effects – 5% GI signs
- Use fish > flax sources for omega 3

EFA Considerations

- Salmon is over-fished and quality of fish-farming is variable
- Consider smaller non-predatory, renewable, high fat species (anchovies, sardines)
- Lack of standardization and poor quality control
- Important to test for heavy metals, ocean pollutants, contamination
- EPA/DHA content listed in mg on label
- Form of fish oil is important - triglyceride most common with relatively low levels of EPA/DHA; free form is best

Glucocorticoids

- Partial to excellent response in 75-97% of atopic dogs, but many side effects
- Try to avoid long term use – use for temporary relief of intense itch or acute and chronic otitis externa
- Long-acting injectable preparation contain molecules that alter solubility → slow release from tissue/prolonged absorption
  - Continuous release → more side effects
  - Cannot 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
  - Use for refractory cases
  - Taper to q 72 hour dosing
- Steroid equivalence converter: www.mdcalc.com/steroid-conversion-calculator

My Experiences with Glucocorticoids

- Works very well in almost all patients
- Inexpensive
- Side effects are often limiting factor!
  - PU/PD/PP – have owners be consistent with food and water offerings, pick up water bowl overnight, feed out of food puzzles to slow consumption, offer carrots, apples, high fiber snacks, taper more quickly
- Best choice for acute or chronic otitis externa (short term), pedal furunculosis, and severe inflammatory lesions
- Best not to use concurrently with oclacitinib
- Monitoring (no specific FDA recommendations)
  - Baseline CBC/Chem then at 1 month, then every 6 months with urinalysis

Cyclosporine

- 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

Side effects

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

My Experiences with Cyclosporine

- Works very well but not in all patients
- Consider for patients requiring chronic therapy
- Large capsule and may be costly for large dogs- consider modified liquid (Cyclavance^{TM}); caution with drugs that affect P450 enzyme system
- Side effects are often transient and reversible
    - Gastrointestinal - store frozen, give with food long term, consider concurrent metoclopramide or maropitant when initiating therapy, increase to target dose over 5-7 days
    - Gingival hyperplasia - uncommon, but can be exacerbated in predisposed breeds (boxers, bull dogs, WHWT)
- No increased risk of neoplasia
- Consider Apoquel, Cytopoint, or glucocorticoids for first three weeks due to slow onset
- Can often lower dose to every 48 hours (36% in one study)
- Works well for otitis externa, pedal furunculosis, and more inflammatory lesions
- Monitoring (no specific FDA recommendations) - baseline CBC/Chem then at 1 month, then every 6 months

Oclacitinib and IL-31

- Cytokines Involved in canine allergic skin disease are secreted from activated T-lymphocytes
- Oclacitinib Mechanism of Action
    - Inhibits Janus kinase (JAK) enzymes - JAK1 and JAK3
    - Inhibits pro-inflammatory and pro-allergic Th2 cytokines that use JAK1
    - Minimal impact on Th1 cytokines from JAK2 which function inn hematopoiesis and innate immunity

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
- Recent history of demodicosis
- Deep infection
- Neoplasia
- Severe otitis externa
- 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

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 Experience with Cytopoint®
- Works very well but not in all patients
- Minimal (if any) side effects
- Lasts anywhere from 3-6 weeks
- When I use the most
- Young dogs (< 12 months)
- During diet trial or when initiating ASIT to relieve pruritus
- For allergy flares on other therapies
- If concurrent neoplasia or comorbidity

Address Immunological Imbalance

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
- Response rates (multiple studies)
  - Excellent : 20-38%
  - Partial: 60-100%
  - Poor: About 20%
- 4-12 months for benefit of ASIT
- Goal is improved quality of life, fewer infections, 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 and other pathways relevant to CAD
- Fewer irrelevant cross reacting allergens (↓ false positive reactions)
- More reliable for *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 sensitivity and specificity
- More false positive reactions due to cross reactive carbohydrate determinants and use of mixed monoclonal or polyclonal anti-canine IgE
- Only measures circulating IgE; does not account for other allergic pathways
- 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 control 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

My Ideal Strategy for CAD
- Year-round effective parasite control (isoxazoline)
- Topical therapies to address barrier function and infection (Douxo® S3 Pyo shampoo +/- Dermoscent® or AtopiVet spot-on)
- EFA supplementation or skin support diet
- ASIT for long term control with use of Apoquel® or Cytopoint® as needed during induction or for allergic flares

Future Directions in the Management of CAD
- Intralymphatic immunotherapy
- Further kinase inhibitor and monoclonal antibody development
- Skin barrier targeted treatments
- Role of skin microbiome in disease
- Probiotics
- Diet

<u>Conclusions</u>
- 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
- Many different safe and effective therapies to control symptoms
- Consider referral and immunotherapy for long term management

References Available Upon Request