Pruritus

“An unpleasant sensation that provokes the desire to scratch”

- One of the five cutaneous sensations
- Physiologic or pathologic basis
- Central, peripheral, or combined initiation
- Is it itchy or painful?

Neurogenic Skin Disorders

- Acral lick dermatitis
  - Central, spinal, or peripheral origin
- Acral mutilation syndrome
- Lumbosacral stenosis
- Caudal Occipital Malformation (Chari Syndrome)
- Tail dock, declaw, etc neuroma
- Trigeminal neuritis
- Others

Peripheral Neuritis

- Rare
- Impossible to document antemortem
  - Sudden onset
  - Intense UNILATERAL pruritus (pain?)
  - Poor response to steroids
    - Apoquel?
- Difficult to treat
Spinal Neuritis
- Uncommon
- Variable speed on onset and progression
- Typically symmetrical
- Variable response to steroids

Treatments for Neuropathies
- Amitriptyline: 1-2 mg/kg q12h
- Gabapentin: 5-10 mg/kg q8h
- Pregabalin: 2-4 mg/kg q12h
- Phenobarbital: 1-3 mg/kg q12-24h

Behavioral Skin Disorders

<table>
<thead>
<tr>
<th>DOG</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acral lick derm</td>
<td>Traumatic alopecia</td>
</tr>
<tr>
<td>Flank sucking</td>
<td>Tail sucking</td>
</tr>
<tr>
<td>Foot licking</td>
<td>Barbering</td>
</tr>
<tr>
<td>Self-nursing</td>
<td></td>
</tr>
<tr>
<td>Tail biting</td>
<td></td>
</tr>
</tbody>
</table>

Foot Licking

Differential Diagnosis
- Allergy
- Atopy
- Food hypersensitivity
- Contact
- Drug (?)
- Malassezia pododermatitis
- Demodicosis
- Helminthosis
- Hookworms
- Pelodera

Perineal Licking
- Psychogenic or pathologic basis
- Pathologic causes most common
  - Anal sac disease
  - Malassezia dermatitis
  - Mucocutaneous pyoderma

Urticaria-Angioedema-Anaphylaxis
- Potentially life threatening condition
- Result of sudden and massive mast cell degranulation
  - Immunologic or non-immunologic causes
  - Superficial, middle, or deep vascular plexuses targeted
Common Causes of Urticaria

- Insect stings/bites
- Foods
- Vaccinations
- Drugs

Treatment

- Identify cause!!
- Medical treatments
  - None
  - Antihistamines
  - Glucocorticoids
  - Epinephrine
  - Shock treatments
- Prevent re-exposure!!

Vaccine-induced Dermatopathies

- Urticaria-angioedema-anaphylaxis complex
- Vasculitis
  - Focal pinnal necrosis
  - Focal alopecia
  - Generalized disease

Treatment

- Avoid vaccination
- Different manufacturer?
- Medical management
  - Steroids
    - Systemic
    - Topical
  - Pentoxifylline
  - Tacrolimus
  - Ear crop

Relative Steroid Potency

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone acetate</td>
<td>1</td>
</tr>
<tr>
<td>Hydrocortisone acetonate</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>5</td>
</tr>
<tr>
<td>Isotretinone</td>
<td>14</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
</tr>
<tr>
<td>Betamethasone valerate</td>
<td>30</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>231</td>
</tr>
</tbody>
</table>

Tresaderm®: 5 drops/ear q12h 20 drops = 1.0 mg of dexamethasone = 0.25 mg prednisolone
Posatex™: 4 drops/ear q24h 8 drops = 0.2 mg of mometasone = 11.6 mg prednisolone

Tacrolimus
**Tacrolimus**

0.03% and 0.1% ointments

Macrolactam immunomodulator

A. Decreased T lymphocyte maturation and activation
B. Decreased cytokine expression in T cells, Langerhans’ cells, keratinocytes, mast cells, and eosinophils
C. Decreased production of IL-2, IL-3, IL-4, IL-5, TNF-α

No cutaneous atrophy

Burning sensation

Avoid UVB/UVA


**Uses for Tacrolimus (Protopic®)**

- Atopic dermatitis
- Contact hypersensitivity
- Lichenoid dermatoses
- “Autoimmune” disorders
  - Vitiligo
  - Discoid lupus
  - Pemphigus erythematosus
  - Cutaneous lupus erythematosus
  - Alopecia areata, pseudopelade


**Pentoxifylline**

Multiple anti-inflammatory and immunomodulatory properties:

↑ RBC/WBC deformability

↓ platelet aggregation

↓ IL-1, IL-4, IL-12, TNF-α, T and B cell activation, NK cell activity, T cell adherence to keratinocytes


**Pentoxifylline**

- 25 mg/kg q12h
- Infrequent side effects (nausea, inappetence, vomiting)
- Give with food
- Slow onset (4 weeks)


**PTX-Responsive Dermatoses**

- Atopic dermatitis
- Contact hypersensitivity
- Vasculitis
- Pinnal thrombovascular necrosis
- Lupoid onychodystrophy
- Familial dermatomyositis
- Cutaneous lupus erythematosus
- Erythema multiforme


**Atopic Dermatitis**

- PTX-responsive dermatoses
- Eczema
Definitions

Atopic Dermatitis
A genetically predisposed inflammatory and pruritic skin disease with characteristic clinical features associated with IgE antibodies most commonly to environmental allergens.

Atopic-like Dermatitis
A genetically predisposed inflammatory skin disease with clinical features identical to atopic dermatitis in which IgE antibodies to environmental allergens are not demonstrable.

Initial Sensitization Process

Cytokines: The Common Denominator in Allergic Skin Disease

Adaptive Immune Response
- IL-2 (JAK1, JAK3)
- IL-4 (JAK1, JAK3)\(^1,2\)
- IL-5 (JAK2)\(^1\)
- IL-9 (JAK1, JAK3)
- IL-10 (JAK1, Tyk2)
- IL-11 (JAK1)
- IL-12 (JAK2 and Tyk2)\(^1\)
- IL-13 (JAK1)\(^1\)
- IL-25
- IL-31 (JAK1, JAK2)\(^1\)
- INF-gamma (JAK1, JAK2)
- RANTES (JAK independent)

Innate Immune Response
- TNF-alpha (JAK independent)
- IL-5 (JAK independent)
- IL-6 (JAK1, JAK2, Tyk2)
- IL-18 (JAK independent)\(^1\)
- GM-CSF (JAK2)\(^1\)
- TBLP (JAK1, 7)\(^2\)
Clinical Disease

Mast Cell Activation
- Various triggers
  - Non-immunologic
  - Immunologic: IgE, IgG
- Multiple mediators released
  - Histamine
  - Leukotrienes
  - Prostaglandins
  - Proteases
  - Cytokines
  - Etc.

Histamine Receptor Activities
- H1: ↑ vascular permeability, alter pruritus via sensory nerves
- H2: ↑ gastric acid secretions, smooth muscle relaxation, inhibit antibody synthesis, T-cell proliferation and cytokine production
- H3: Neurotransmitter in CNS
- H4: Regulates neutrophil release from bone marrow, mast cell chemotaxis

Atopic Dermatitis- Pathogenesis
- Genetic predisposition
- Altered epidermal barrier
- ↓ Lipids/ceramides in stratum corneum
- Altered epidermal barrier function
- ↑ Percutaneous antigen absorption
- ↑ Antigen presenting cells
Epidermal Lipids

WHAT ARE THEY?

Epidermal Lipids

Corneocyte layer

Lipids

Corneocyte layer

Lipids

Courtesy: Virbac

Epidermal lipid defects in skin disease

Healthy dog

Atopic dog

Courtesy: Virbac

Atopic Dermatitis- Pathogenesis

Mast cell/basophil releasability
Overactive phosphodiesterase isoforms
Keratinocytes (↓ defensins, colonization)
Stem cell factor (↑ in atopic and normal skin)
Fat metabolism (↓ absorption/↑ clearance; Δ 6 + Δ 5 desaturase deficiency)

Pruritic Threshold

Canine Atopic Dermatitis

- Early age at onset: 6 – 36 months
- Breed predisposition – familial history
- Initially seasonal
- Progressive in clinical severity and duration of disease
Canine Atopic Dermatitis

- Nonlesional pruritus usually
- Pruritus stops with appropriate glucocorticoid administration
- Multiple routes for re-exposure
  - Skin
  - Lungs
  - GI tract

Prednisolone* Responsiveness

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated Atopy: 99%</td>
<td>Food allergy: 80-90%</td>
</tr>
<tr>
<td>Food Allergy: 10-20%</td>
<td>Drug allergy: 95%</td>
</tr>
<tr>
<td>Early insect allergy: 99%</td>
<td>Scabies: 99%</td>
</tr>
<tr>
<td>Mild contact dermatitis: 99%</td>
<td>Malassezia derm: 95%</td>
</tr>
<tr>
<td>Etc.</td>
<td>Bacterial hypersensitivity: 95%</td>
</tr>
<tr>
<td>Etc.</td>
<td>Hormonal hypersensitivity: 95%</td>
</tr>
<tr>
<td>Etc.</td>
<td>Behavioral disorders: 95%</td>
</tr>
<tr>
<td>Etc.</td>
<td>Chronic insect allergy: 50%</td>
</tr>
</tbody>
</table>

*Dogs: 1 mg/kg q24h
Cats: 2 mg/kg q24h

Clinical Features of Canine Atopy

- Recurrent otitis externa
- Facial pruritus ± ear disease
- Pedal pruritus
- Axillary ± inguinal pruritus
- Generalized pruritus

Clinical Features of Canine Atopy

- Staphylococcal pyoderma
- *Malassezia* dermatitis
- Pyotraumatic dermatitis
- Acral lick dermatitis
- Anal sacculitis
- Hyperhidrosis

Atopic Dermatitis - Diagnosis

- History
- Physical examination
- Exclusion
  - Clinical testing
  - Skin biopsy
- Allergy testing – For allergens selection and not for diagnosis!!
Methods of Allergy Testing

- None: Use regionalized “off the shelf” extracts
- In vivo methods
  - Dechallenge/challenge
  - Prick testing
  - Intradermal testing
  - Patch testing
- In vitro methods
  - Basophile degranulation test
  - Serologic allergy tests

RESPIT™
Regionally-specific immunotherapy

- Standardized allergen extracts defined by geographic region
- Inclusion based on
  - Aerobiology
  - Allergenicity
  - Cross-reactivity

Intradermal Skin Testing

- “Gold standard” for atopy
- Can be used in all species
- Little or no value in other allergic conditions
- Labor intense
- Expensive

Prerequisites for Intradermal Testing

- Test in correct season: 60 day window?
- Test non-inflamed skin
- Adequate drug withdrawal
IDST Drug Withdrawal Requirements

- Oral steroids: 3 weeks minimum
- Injectable steroids: 6 weeks minimum
- Antihistamines: 2 weeks
- Nutraceuticals: 2 weeks
- Cyclosporine: None?
- Apoquel: None
- CADI: None

Serological Allergy Test Methods

- Radioallergosorbent test (RAST)
- Enzyme-linked immunosorbent test (ELISA)
- Liquid-phase enzymoimmunometric assay (VARL)
- High-affinity Fc epsilon receptor α-chain detection system (HESKA)

Serological Allergy Testing

- Rapid and easy
- Minimal drug interference
- Less seasonal influence
- Frequent “false-positives”
- Lab errors?
- Subclinical allergies?
- Parasitism can induce false positives
- Mite cross-reactions

Serology Testing - Accuracy

<table>
<thead>
<tr>
<th>Lab</th>
<th>FBS</th>
<th>CAIb</th>
<th>SPFCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>33.3</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>0.7</td>
<td>3.5</td>
</tr>
<tr>
<td>C</td>
<td>30.8</td>
<td>27.7</td>
<td>28.9</td>
</tr>
<tr>
<td>D</td>
<td>5</td>
<td>1.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Agreement between allergen-specific IgE assays and ensuing immunotherapy recommendations from four commercial laboratories in the USA
Plant, JD, et al

- 10 atopic dogs
- Samples sent to Bio-Medical Services, VARL, Heska, and IDEXX
- Diagnostic agreement across all dogs and all laboratories: 70%
  - Agreement expected by chance: 66%
- ASIT agreement across dogs and laboratories: 72%
  - Agreement expected by chance: 69%
- Highest level of chance-corrected agreement between Heska and IDEXX

Food Hypersensitivity

- Genetic predisposition not required
- Allergens
  - Water-soluble proteins and glycoproteins
  - ≥4,000 Daltons??
- Variable clinical presentations
  - Skin
  - Non-skin
  - Combination

Reported Allergens in the Dog

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Grains</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td>Corn</td>
<td>Potatoes</td>
</tr>
<tr>
<td>Chicken</td>
<td>Oats</td>
<td>Kidney beans</td>
</tr>
<tr>
<td>Pork</td>
<td>Rice</td>
<td>Pasta</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Wheat</td>
<td>Dairy products</td>
</tr>
<tr>
<td>Turkey</td>
<td>Wheat</td>
<td>Commercial dog food</td>
</tr>
<tr>
<td>Soy</td>
<td></td>
<td>Commercial dog treats</td>
</tr>
<tr>
<td>Horse meat</td>
<td></td>
<td>Chocolate</td>
</tr>
<tr>
<td>Lamb</td>
<td></td>
<td>Food additives</td>
</tr>
<tr>
<td>Fish (various)</td>
<td></td>
<td>Food preservatives</td>
</tr>
<tr>
<td>Eggs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cross-Reacting Foods in Humans

Dairy products: caseins, bovine serum albumins, lactoglobulins
Fish: parvalbumin
Crustaceans
Poultry: chicken serum albumin
Milk: cow, goat, sheep
Egg: ovalbumin, ovomucoid
Wheat, barley, rye

Food Hypersensitivity

Source of exposure
- Daily ration
- Treats & supplements
- Medications
- Scavenged/hunted foods
- “Digested” allergens
- Matter in drinking water

Clinical Features: Canine Food Hypersensitivity

- Atopic-like pruritus
- Persistent urticaria
- Recurrent or persistent otitis externa
- Recurrent episodes of acute moist dermatitis
- Lumbosacral pruritus
- Scabies-like pruritus
- Generalized pruritus
Food Hypersensitivity - Diagnosis

- History
- Physical
- Diagnostic exclusion
- Serologic testing?
- Food dechallenge/challenge

Serologic Testing for Food Hypersensitivity

- Validity?
- Challenge testing required

NutriScan Test

- Not for testing for food allergies, but rather tests for food sensitivities and intolerance.
- Food allergy is a more immediate reaction mediated by production of IgE and IgG antibodies.
- Food sensitivity and intolerance measures a more delayed body response to offending foods by measuring production of mucosal IgA and IgM antibodies.

NutriScan - Dog Food Sensitivity Kit

<table>
<thead>
<tr>
<th>Panel 1:</th>
<th>Panel 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td>Chicken Eggs</td>
</tr>
<tr>
<td>Corn</td>
<td>Barley</td>
</tr>
<tr>
<td>Wheat</td>
<td>Millet</td>
</tr>
<tr>
<td>Soy</td>
<td>Oatmeal</td>
</tr>
<tr>
<td>Cow’s Milk</td>
<td>Salmon</td>
</tr>
<tr>
<td>Lamb</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Venison/Deer</td>
<td>Rice</td>
</tr>
<tr>
<td>Chicken</td>
<td>Quinoa</td>
</tr>
<tr>
<td>Turkey</td>
<td>Potato</td>
</tr>
<tr>
<td>White Fish</td>
<td>Peanut/Peanut Butter</td>
</tr>
<tr>
<td>Pork</td>
<td>Sweet Potato</td>
</tr>
</tbody>
</table>

Dietary Dechallenge & Challenge

- Modify entire diet
  - Water
  - Food
  - Flavored chew toys
  - Snacks: commercial, accidental, natural
  - Oral medications: Just flavored or all?
- Modify household’s lifestyle
Lifestyle Changes
- Eliminate access to snacks
- Visitors
- Toddlers, senior citizens
- Litter boxes, barns, etc
- Kitchen @ mealtimes
- No hunting
- Leash walking only
- Basket muzzle?

Time Course for Testing
- Initial test period: 4 weeks
- Results:
  - No change in level of pruritus: Not food allergy
  - 50% or greater improvement: probably food allergy
    - Continue diet until pruritus disappears entirely
    - Continue diet until pruritus is reduced to its lowest level
- Prove response by challenge with original diet and snack foods

Dietary Dechallenge & Challenge
- Dietary history required for accurate formulation of test diet
  - At onset only?
  - Entire course of disease?
- Types of diets available
  - Home cooked
  - Commercial
    - OTC limited ingredient diets
    - Veterinary limited ingredient diets
    - Altered molecular weight foods

Home cooked Diets
- **Proteins**
  - Tofu
  - Rabbit
  - Venison
  - Ostrich
  - Exotic fowl
  - Fish
  - Shell fish

- **Carbohydrates**
  - White potatoes
  - Sweet potatoes
  - Brown rice
  - White rice
  - Barley
  - Lentils
  - Pinto beans

Commercial Limited Ingedient Foods

Veterinary Prescription Diets
Hydrolyzed “Hypoallergenic” Foods

Starch, hydrolyzed soy protein isolate, vegetable oil, partially hydrogenated canola oil, corn oil

Starch, hydrolyzed Chicken Liver, Soybean Oil, Hydrolyzed Chicken

Brewers rice, hydrolyzed soy protein, chicken fat, natural flavors, chicken fat, dried beet pulp, vegetable oil

Maize starch, feather hydrolysate, copra oil, soya oil, fructo-oligo-saccharides, fish oil

Thierry Olivry, DrVet, PhD
Professor, Immunodermatology

- At MVIS, I presented a study using sera from chicken-allergic dogs with low, medium and high IgE against chicken, after cross-reacting to duck and turkey. Interestingly, one of the 3 dogs had IgE that recognized the hypoallergenic hydrolysed chicken liver but not the native chicken liver. So the feather hydrolysate appeared digested enough to have different proteins than the meat is not fully poultry species, e.g. the high level of hydrolysis was confirmed independently by HPLC at the 2015 AOVS/ECVD Congress: the poultry feather hydrolysate has not detected proteins that reacted with patients.

- At the Congrès de l’APDC, a study was presented (published yet) with 30 sera which had high IgE levels against cows. 10% of the sera (4/10) that with the highest level of IgE against cows had a positive test against the high protein corn starch present in the chicken hydrolysate. Later studies confirmed that these hydrolysates are the best candidates for an effective vaccination against high protein corn starch (present or mainly antigenic protein). These cord (4/10) are typically non-pathogenic in human allergic patients. Perhaps a few (10) are pathogens in dogs and other species, but this is not yet known.

- It is important to remember that these studies are only dealing with IgE present in the dog sera, these are not necessarily orally-eaten. As an allergy vaccine, we published in 2015 that the chicken feather hydrolysate can be eaten by healthy subjects and does not cause any adverse effects. Later studies confirmed that these hydrolysates are the best candidates for an effective vaccination against high protein corn starch (present or mainly antigenic protein). These cord (4/10) are typically non-pathogenic in human allergic patients. Perhaps a few (10) are pathogens in dogs and other species, but this is not yet known.

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**Dietary Dechallenge & Challenge**

- Determine significance of any change rechallenge
- Mix original food into special diet
  - Flair: 15 minutes → 7 days
  - No change
  - Incorrect diagnosis
  - Different allergen: treat, etc

**Long-term Management**

- Continue feeding diet used for testing
  - Home cooked diet: balance for nutritional completeness
  - Commercial diet: read label each time a new supply is purchased
- Do individual ingredient challenges to determine which ingredient(s) is the allergen
- Select new commercial food based on challenge testing

**Allergies Are Forever!!**