Antipruritic Therapy

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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?

Commonly Used Treatments

- Avoidance
- Topicals
- Medical treatments
  - Glucocorticoids
  - Antihistamines
  - Psychotropic agents
  - Nutraceuticals
  - Immunomodulatory agents
- Immunotherapy

Topical Antipruritic Therapy

- Usually an adjunctive treatment
- Useful in
  - Removing surface allergens
  - Removing surface bacteria or yeast
  - Hydrating the skin
  - Providing some anti-inflammatory and antipruritic activity

Topical Antipruritic Therapy - Regional

- Various application methods
  - Creams & ointments
  - Sprays
  - Mousse
- Common active ingredients
  - Pramoxine
  - Glucocorticoids
  - Tacrolimus
  - Miscellaneous
**Pramoxine**

- Local anesthetic
- Nonirritating, nonsensitizing
- No methemoglobinemia or Heinz body issues
- 1% shampoo, rinse, spray, lotion or mousse

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**Topical Glucocorticoids**

- Great variation in potency
- Only 1 straight steroid preparation licensed in veterinary medicine
- Frequency of application and potency of product impacts cutaneous and systemic side effects

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**Relative Steroid Potency**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency</th>
<th>Duration (HPA)</th>
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<tbody>
<tr>
<td>Hydrocortisone acetate</td>
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<tr>
<td>Hydrocortisone aceponate</td>
<td>&gt;30</td>
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<tr>
<td>Prednisolone, prednisone</td>
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<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>12-36</td>
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<tr>
<td>Triamcinolone acetonide</td>
<td>&gt;5-10</td>
<td>12-36</td>
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<tr>
<td>Isopropenol</td>
<td>14</td>
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<tr>
<td>Dexamethasone</td>
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<tr>
<td>Betamethasone valerate</td>
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<td>&gt;48</td>
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<tr>
<td>Fluocinolone</td>
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<td>Mometasone furoate</td>
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</table>

*Useful Otic Steroids*

- Hydro B – 1020 – Hydrocortisone acetate
- easOtic® - Hydrocortisone aceponate
- Tresaderm® - dexamethasone
- Otomax™, Osurina® - betamethasone
- Anamax® - triamcinolone
- Surolan® - prednisolone
- Mometamax™, Posatex™, Claro™ - mometasone

*Dosage and Dilutions:*

- **Tresaderm®:** 5 drops/ear q12h 20 drops = 1.0 mg of dexamethasone = 6.25 mg prednisolone
- **Posatex™:** 4 drops/ear q24h 8 drops = 0.2 mg of mometasone = 11.6 mg prednisolone
3 month-old dog: 6 days of twice daily Betagen spray

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
$$$$$
OTC First Aide Remedies

Topical Antipruritic Therapy – Whole Body
- Rinses
- Soaks
- Shampoos
  - Hypoallergenic, moisturizing
  - Colloidal oatmeal
  - Pramoxine
  - Hydrocortisone
  - Hydrocortisone + pramoxine
- Barrier replenishment

Colloidal Oatmeal
- Moisturizing (humectant)
- Antipruritic
- Nonirritating, nonsensitizing
- Shampoo (Epi-Soothe,™ Virbac)
- Rinse/soak (Aveeno® flakes; 2 tablespoon/gallon [30 ml/4 liters] cool water)

Moisturizers
- Rehydrate, soften, lubricate, barrier repair, remove allergens/irritants
- Emollients and humectants (“NMF” = lactic acid, urea; colloidal oatmeal)
- Hydra Pearls™ shampoo, rinse (Vétoquinol)
Lipid-replacement therapy

After topical application, the SLC diffuses through SC to the deeper layers of the epidermis and enhances the lipid synthesis
**Allerderm spot-on**

EM observation on treated sites in atopic dogs

Lower part of stratum corneum

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**Systemic Therapy**

- Dozens of available products
- Various mechanisms of action

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**Oral Treatments**

- Glucocorticoids
- Antihistamines
- Psychotropic agents
- Nutraceuticals
- Immunomodulatory agents
- Immunosuppressive agents

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**Medical Treatment Options**

**Dog**

<table>
<thead>
<tr>
<th>Duration (months)</th>
<th>Oral Steroids</th>
<th>Antihistamines</th>
<th>Immunotherapy</th>
<th>Cyclosporine</th>
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<tr>
<td>0-2</td>
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**Medical Treatment Options**

**Cat**

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**Rational Steroid Therapy**

- Use carefully
- Use short-acting oral drugs only
- Administer daily beyond clinical remission
- Maintain remission with EOD administration
- Reduce dosage to lowest acceptable level – LEAVE SOME ITCH!!
Glucocorticoid Therapy

Anti-inflammatory prednisolone doses

- **Dog:** 1.0 mg/kg q24h
- **Cat:** 2.0 mg/kg q24h
- **Horse:** 2.0 mg/kg q24h

Alternate drug conversion factors

- Methylprednisolone: 0.8
- Dexamethasone: 0.1
- Triamcinolone: 0.2

Termaril-P

- **Trimeprazine tartrate:** 5 mg
- **Prednisolone:** 2 mg

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<tr>
<th>Weight of Dog</th>
<th>Initial Dosage</th>
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<td>Up to 10 lb</td>
<td>1/2 tablet, twice daily</td>
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<td>11-20 lb</td>
<td>1 tablet, twice daily</td>
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<td>21-40 lb</td>
<td>2 tablets, twice daily</td>
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<td>Over 40 lb</td>
<td>3 tablets, twice daily</td>
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After 4 days, reduce dosage to 1/2 of the initial dose or to an amount just sufficient to maintain remission

Antihistamine Therapy

- Hundreds available: H1, H2, H3, and H4
- Unpredictable efficacy
  - Response determined by rotating 7-14 day drug trials
- May lessen or eliminate pruritus
- Safe long term
Antihistamine Groups

- Ethanolamines (clemastine, diphenhydramine)
- Ethylenediamines (pyrilamine, tripelennamine)
- Phenothiazines (promethazine, trimeprazine)
- Piperazines (hydroxyzine)
- Propylamines (brompheniramine, chlorpheniramine)
- Others (cyproheptadine, loratidine, terfenadine)
- Heterocyclics (amitriptyline, doxepin)


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<tr>
<th>Drug</th>
<th>% S</th>
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<tr>
<td>Chlorpheniramene</td>
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<tr>
<td>Diphenhydramine</td>
<td>6.7</td>
<td>15.6</td>
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<tr>
<td>Hydroxyzine</td>
<td>6.7</td>
<td>17.8</td>
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Contraindications for Antihistamine Therapy

- Glaucoma
- Retentive disorders
- Seizure disorders
- Hepatic dysfunction
- Cardiac arrhythmias
- Pregnancy
- Drug interactions
- Competitive sports, etc

Psychotropic agents

- Central modification of pruritic stimulus
- Separate peripheral actions
- Same contraindications as antihistamines
- Potentially useful agents
  - Amitriptyline
  - Doxepin
  - Phenobarbital

Neural Focused

- Amitriptyline: 1-2 mg/kg q12h
- Gabapentin: 5-10 mg/kg q8h
- Pregabalin: 2-4 mg/kg q12h

Potentially Effective Drugs - Dog

- Cetirizine: 1 mg/kg q24h
- Chlorpheniramene: 0.4 mg/kg q8h
- Clemastine: 0.05-0.1 mg/kg q12h
- Diphenhydramine: 2.2 mg/kg q8h
- Hydroxyzine: 2.2 mg/kg q12h
- Loratidine: 1-2 mg/kg q24h
- Amitriptyline: 1-2 mg/kg q12h
- Pentoxifylline: 25 mg/kg q12h
### Potentially Effective Drugs - Cat

- **Chlorpheniramine:** 2-4 mg/cat q12h
- **Cetirizine:** 5 mg/cat q24h
- **Clemastine:** 0.68 mg/cat q12h
- **Diphenhydramine:** 2.2 mg/kg q12h
- **Loratadine:** 5 mg/cat q24h
- **Amitriptyline:** 0.5-1.0 mg/kg q12h
- **Cyproheptadine:** 2 mg/cat q12h

### Omega-3 and Omega-6 Fatty Acids

![Omega-3 and Omega-6 Fatty Acids](image)

### Eicosanoids and Fatty Acids Made Simple

![Eicosanoids and Fatty Acids Made Simple](image)

### Side Effects of Omega-3/Omega-6 Supplements

- *Diarrhea*  
  Lethargy
- **“Fish breath”**  
  Increased pruritus
- **Belching**  
  Urticaria
- **Vomiting**  
  “Greasy”
- **Weight Gain**  
  Pancreatitis
- **Bleeding**
**Fatty Acid Supplements**

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Dog Dosage</th>
<th>Cat Dosage</th>
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</thead>
<tbody>
<tr>
<td>Derm Caps</td>
<td>Per label</td>
<td>Per label</td>
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<tr>
<td>EPA</td>
<td>40 mg/kg</td>
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<tr>
<td>GLA</td>
<td>&gt;40 mg/kg</td>
<td>&gt;8 mg/kg</td>
</tr>
<tr>
<td>IAMS Foods</td>
<td>Per label</td>
<td>Per label</td>
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</table>

**Derm Defense Diet**

- Proprietary complex of bioactives and phytoneutrants
- High levels of omega-3 & 6 fatty acids
- Clinically proven antioxidants, including vitamin E
- No corn, chicken by product meal, artificial colors, flavors or preservatives

**Phosphodiesterase Inhibitors (Pentoxifylline)**

- Multiple anti-inflammatory and immunomodulatory properties
  - ↑ RBC/WBC deformability
  - ↓ Platelet aggregation
  - PDE inhibition
  - ↓ IL-1, IL-4, IL-12, TNF-α, T and B cell activation
  - NK cell activity, T cell adherence to keratinocytes

**Pentoxifylline Precautions**

- Bleeding problems
- Liver/kidney disease
- Pregnancy
- Nursing neonates
- Insulin therapy

**Drug Combinations**

- Simultaneous administration of different modes of action can:
  - Make ineffective drugs effective
  - Increase efficacy beyond each individual drug
  - Allow significant reduction in steroid dosage
Apoquel® (Oclacitinib)

- A targeted Janus kinase (JAK1 and JAK3) inhibitor
- Inhibits pro-inflammatory and pruritogenic cytokines
- Immunomodulatory vs immunosuppressive
- Dose: 0.4-0.6 mg/kg q12h x14 days then q24h
Long-term compassionate use of oclacitinib in dogs with atopic and allergic skin disease: safety, efficacy and quality of life.
Cosgrove, SB; Cleaver, DM; King, VL; et al.
Vet Dermatol 2015; 26: 171–e35

- Dogs received 0.4–0.6 mg/kg oclacitinib twice a day for 14 days, then once a day for up to 630 days
- Results:
  - Percentage of dogs showing ≥50% reduction from baseline on day 90 was 63.9% for pruritus and 66.4% for dermatitis.
  - Adverse reactions uncommon: Urinary tract cystitis, vomiting, otitis, pyoderma, and diarrhea (>5% of dogs)
  - Haematology and serum chemistry remained normal

A blinded, randomized clinical trial comparing the efficacy and safety of oclacitinib and ciclosporin for the control of atopic dermatitis in client-owned dogs
Little, PF; King, VL; Davis, KR; et al
Vet Dermatol 2015; 26: 23–e8

- Assessed on days 1, 2, 7, 14, 28, 56 and 84.
- Percentage reduction from baseline for owner-assessed pruritus
- Changed from 25.6 to 61.0% in the oclacitinib group compared with 6.5 to 61.5% in the ciclosporin group
- Differences were significant at all time points up to day 28.
- On day 56, ciclosporin-treated dogs showed a similar decrease in pruritus to oclacitinib-treated dogs.
- Three times as many adverse events attributed to gastrointestinal signs were reported in the ciclosporin group
Zoetis’ Target Product Profile for the Caninized Anti-cIL-31 Monoclonal Antibody Therapy

- A novel therapy for atopic dogs
  - Not a pharmaceutical therapy
  - Not a corticosteroid
  - Targets a single cytokine (IL-31)
- Injectable
- Duration of effect of one month
  - Similar to prednisolone and APOQUEL in ability to reduce pruritus
  - Improvement in dermatitis/skin lesions within 7 days
- Unique Safety Profile
  - No immune suppression
  - No production of anti-mAb antibodies
  - No contraindications for other drugs or disease
  - Use in dogs without any limitation to age

What Is the Role of IL-31 in the Animal?

- Regulates aspects of innate as well as adaptive immunity in tissues that are exposed to the environment
- To date, IL-31 has only been identified to play a role in inflammatory diseases
  - Skin disease – atopic dermatitis
  - Lung disease – allergic asthma
  - Bowel diseases – IBD
- Preliminary evidence that IL-31 controls the proliferation and differentiation of cells of non-hematopoietic origin, lending support to the concept that this cytokine plays an integrative role in the proper formation of epithelia

Canine Atopic Dermatitis Immunotherapeutic (Anti-cIL-31 Monoclonal Antibody )

CADI

Significant Improvement in Pruritus Observed at 2 mg/kg

Improvement in Skin Condition Mirrored Decrease in Owner-Assessed Itch at 2 mg/kg
Immunosuppressive Agents

- Azathioprine: 2.2 mg/kg q24h
- Chlorambucil: 0.1-0.2 mg/kg q24h
- Cyclosporine:
  - Dogs: 5 mg/kg q24h
  - Cats: 7 mg/kg q24h

Cyclosporine

Sanimmune® - Novartis (capsules, suspension)
Neoral® - Novartis (capsules, suspension)
Generic (capsules, suspension)
Atopica® - Novartis (capsules, suspension)

Levels in skin higher and persist longer than in blood
Food or no food?

Cyclosporine Effects

Inhibit T lymphocyte
Inhibit antigen presentation
Decreased IL-2, IL-3, IL-4, IL-5, TNF-α, INF-γ
Inhibit mast cell/eosinophil production
Inhibit histamine release
Inhibit neutrophil chemotaxis
Inhibit NK cell activity
Inhibit B lymphocytes

Atopica® Precautions

Killed vaccines
Drugs that affect cytochrome P-450
<4 pounds
<6 months old
Breeding, pregnant, lactating
History of malignant neoplasia
In cats: FeLV, FIV, Toxoplasma tests prior

Cyclosporine Interactions

Increased blood levels – azoles, macrolides, doxycycline, high-dose glucocorticoids, cimetidine, grapefruit juice
Decreased blood levels – anticonvulsants, trimethoprim-sulfa, ciprofloxacin, terbinafine
Avermectins?
Cyclosporine Efficacy

Dogs: 15 – 75%
Cats: Better

Immunotherapy

- True immunologic modulation
- Antigen specific response
- Lifelong treatment required
- Sublingual or subcutaneous administration
- 50-75% response rate
- Response rate influenced by
  - Owner expectations
  - Degree of allergy of patient

“Off the Shelf” Immunotherapy

- Allergy testing not required
  - Center Labs: 1980s
  - RESIP: 2010s
- Most common regional allergens included?
- Injectable or oral immunotherapy options
- Safety?
- Efficacy?

Customized vs. Standardized Immunotherapy for Canine Atopic Dermatitis

Good-excellent response rate (%)

- High dose customized immunotherapy
- Low dose customized immunotherapy
- Standardized immunotherapy

ASIT Administration Schedule

<table>
<thead>
<tr>
<th>Day</th>
<th>Vial 1</th>
<th>Vial 2</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>65</td>
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</table>

After Day 65 injections are given every 3 weeks

Is it time for my allergy shot?
### Annual Cost of Anti-Atopy Treatment 75# Labrador Retriever

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost (CUHA Prices 08/31/2016)</th>
</tr>
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<tbody>
<tr>
<td>Cetirizine</td>
<td>$102.20</td>
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<tr>
<td>Prednisolone (0.25 mg/kg eod)</td>
<td>$22.81</td>
</tr>
<tr>
<td>Apoquel</td>
<td>$689.78</td>
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<tr>
<td>CADI</td>
<td>$1684.80</td>
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<tr>
<td>Atopica</td>
<td>$3285.00</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>$250.00</td>
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</tbody>
</table>