

A microscopic image of skin tissue, showing the epidermal layer with its characteristic wavy, undulating surface and the underlying dermal layer. The image is overlaid with a teal triangle on the right and an orange triangle on the bottom left.

DR.

*Joya*

DOCTOR OF VETERINARY MEDICINE

# Update on Atopic Dermatitis: The New & the Tried & True

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Louisville, Kentucky & Evansville, Indiana

# The New

**Goal:** To explore what we now know about AD in dogs, how to diagnose and what new treatments are being explored and more importantly provides the best relief for our patients.



# History of Atopy

- First called “eczema” in dogs in 1933
  - “Allergic inhalant dermatitis”
  - Canine atopy
  - Now canine atopic dermatitis (AD)
- 
- Most commonly to environmental allergens but non-environmental allergens can trigger flares
  - Extrinsic and Intrinsic forms



# Canine Atopic Dermatitis

- **Definition:** A genetically predisposed inflammatory & pruritic allergic skin dz assoc. with IgE ab's against environmental allergens (extrinsic AD)
- Canine atopic-like dermatitis: clinically identical but w/o demonstrable allergen-specific IgE (intrinsic AD)
- Interplay of genetic and environmental factors affecting both the immunologic response and skin barrier function

# Causes of Atopic Dermatitis

- **Extrinsic AD**

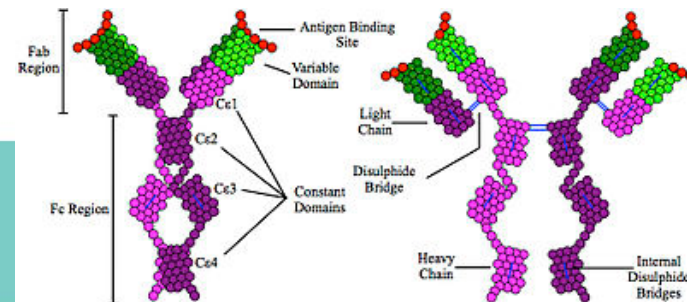
- Presence of IgE
- Heritable epidermal barrier defect
  - Filaggrin gene mutation- assoc. with early onset and severe AD in humans

- **Intrinsic AD (ADL)**

- Absence of IgE
- Nonfamilial and idiopathic
- Possibly early AD prior to allergic sensitization
- English bulldogs

# Pathomechanism

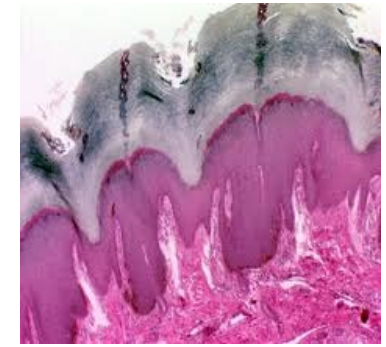
- Primary sensitization to environmental allergens
  - Via respiratory tract & percutaneous absorption
  - Hyperplasia of Langerhans cells found in lesional skin of dogs with AD  
→ initiate the immune response via antigen presentation
- Triggers allergen-specific IgE ab's
  - Bind to mast cells and basophils in dermis
- Secondary exposure results in
  - Degranulation of mast cell or basophil
    - Histamine, serotonin, eosinophil chemotactic factor release
    - Pruritus and erythema



# It's not all about IgE

- 26% of dogs with AD had no demonstrable allergen-specific IgE
  - Hypotheses: Unidentified allergens, early AD, or non-IgE dependent AD
- Non-IgE atotics dependent on
  - T-cell subpopulation polarization
    - Th2 predominant in acute phase
    - Th1 in chronic phase
  - Altered mast cell releasability
- Defective Barrier function also plays a role
  - Increase allergen penetration
  - Increase susceptibility to microbes

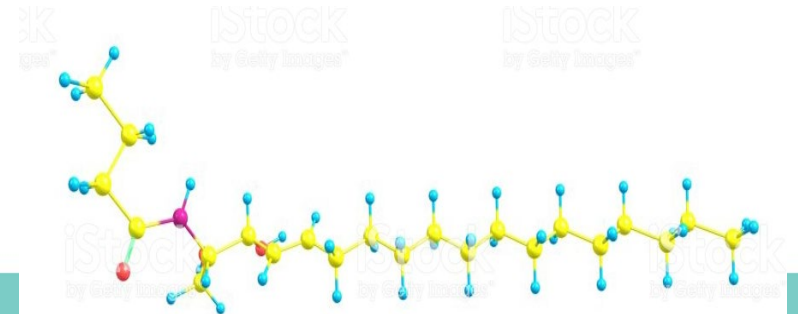
# Barrier Function Abnormalities



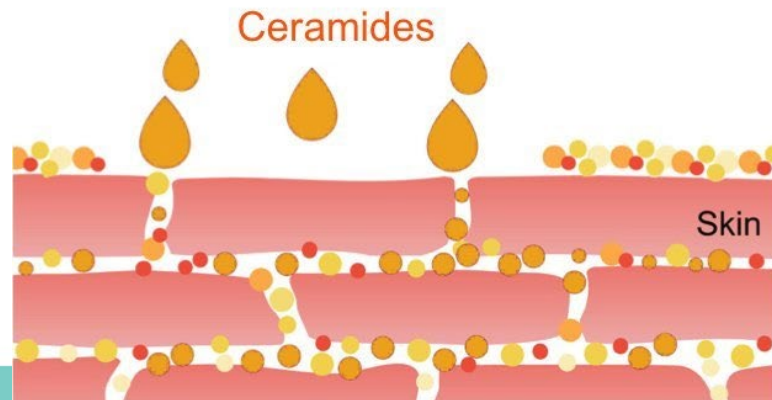
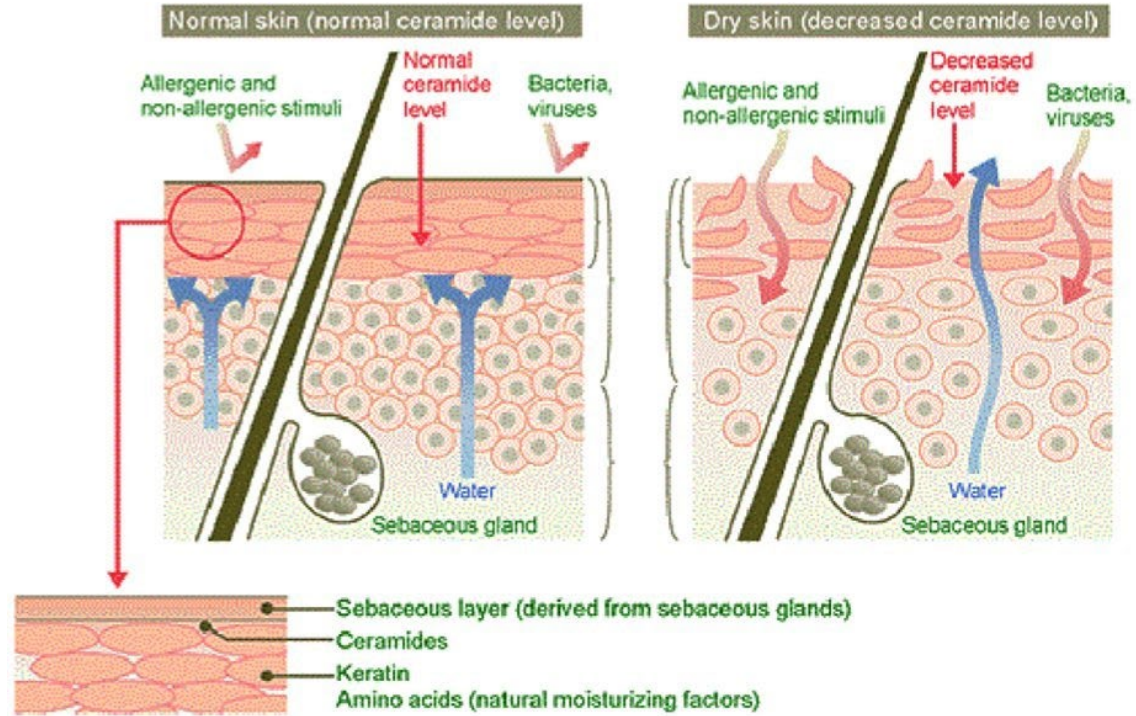
- Inherent and acquired
- Exacerbates severity
- Irregularities in ultrastructure of the upper layers of the epidermis
  - Widening of intracellular spaces
  - Retention of lamellar bodies in corneocytes
  - Fragmented lipid lamellae
- ➡ Results in decrease in epidermal ceramides\*
- Functional abnormalities measured by increased TEWL
  - Increased allergen penetration

# Role of Ceramides

- Deficiency found in AD in humans and dogs
  - Increase TEWL
  - More severe in lesional skin
  - May be primary or acquired?
- Topical and oral lipids aimed at restoring barrier fxn

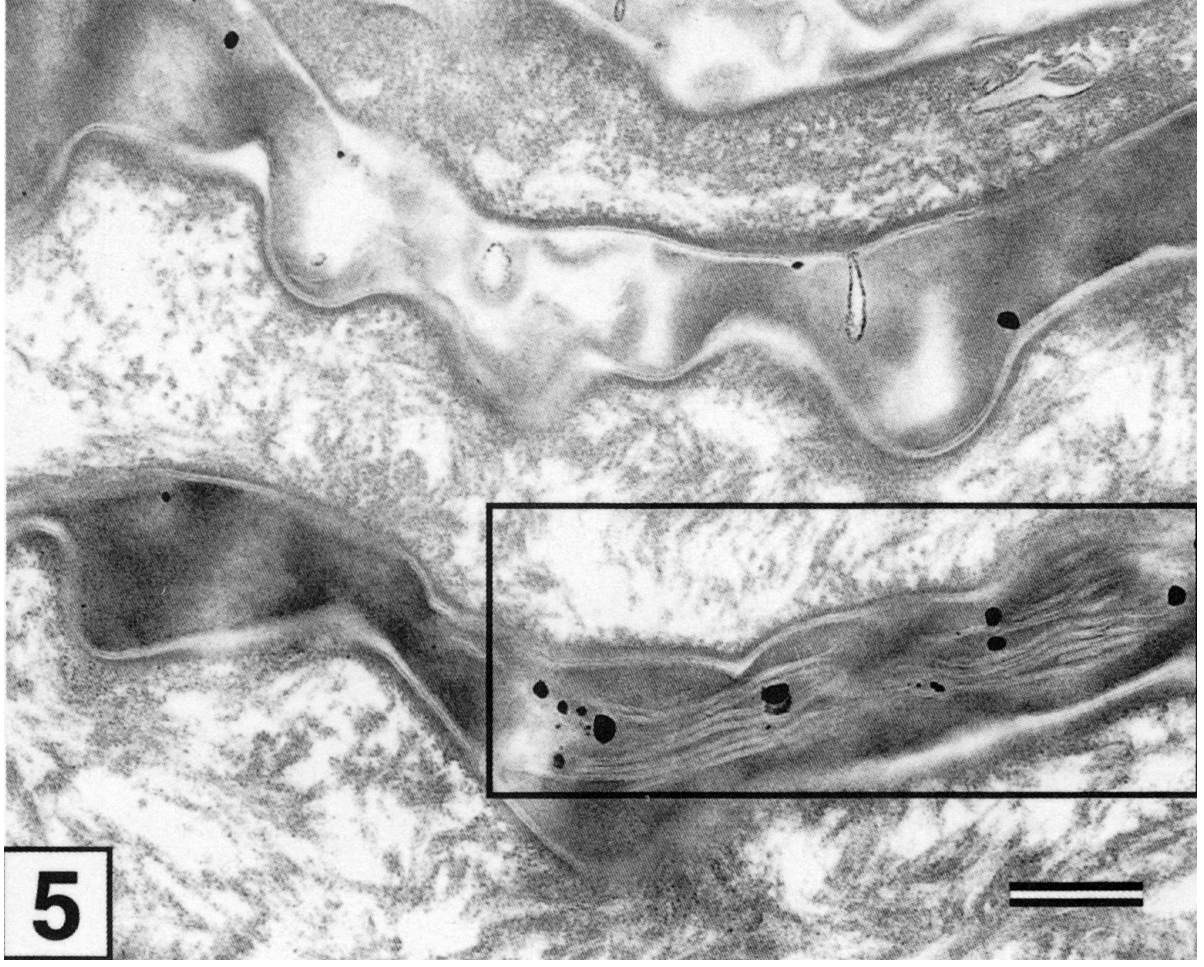
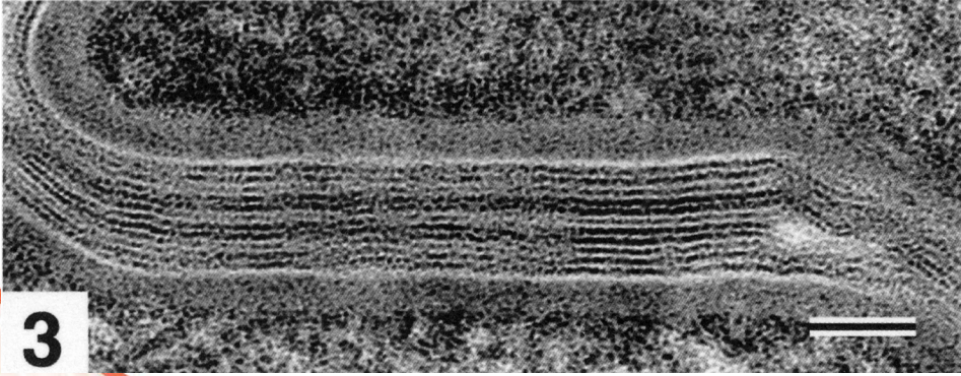


## Comparison between normal and dry skins



Ceramides help repair the skin's natural barrier and help skin retain water.

# Normal vs. AD





# Incidence of Atopic Dermatitis

- Increasing in humans
  - Especially in industrialized countries
    - Microflora Hypothesis- decreased exposure to bacteria, parasites & use of antibacterial detergents alters skin barrier fxn
  - Often assoc. with asthma, hay fever & allergic conjunctivitis
- Inverse relationship btwn endotoxin exposure & development of atopy in dogs
- Decreased risk IF live n rural area, live w/ other animals, & walk in a forest

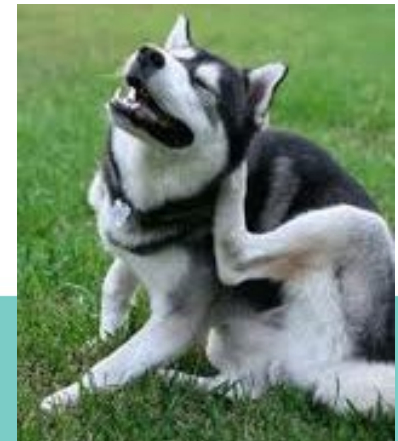
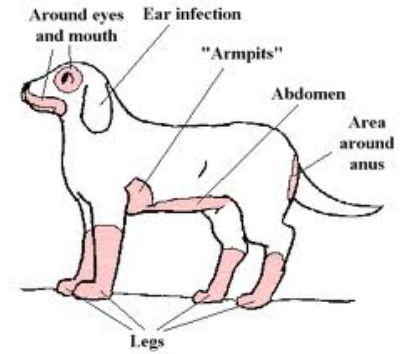
# Clinical Features

- Up to 58% dogs with skin disease
- Age of onset: 6 months to as late as 6 year
- Early onset in highly susceptible dogs in warmer climates
- Increase risk in dogs w/ 4 or more atopic-type skin dzs in first 15 months
- Starts seasonal or nonseasonal
  - 80% of seasonal become nonseasonal
- Predisposed breeds: English Bulldogs, terriers, retrievers and Brachycephalics
- Concurrent food, flea or contact allergy is common



# Clinical Signs

- Nonlesional pruritus is hallmark
- Lesions most commonly affect hairless areas:
  - Axilla, inguinal region, interdigital spaces
  - Muzzle, periocular areas, pinnae
  - Sites of percutaneous absorption of allergens
- Also hyperhidrosis, otitis, conjunctivitis, saliva-staining, lichenification, hyperpigmentation, acral lick granuloma, acute moist dermatitis



- Dogs rarely exhibit seasonal allergic rhinitis or asthma like in humans
- Occasionally reverse sneezing, GI disturbance
- Secondary infections are common





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# What's New in Diagnosis?

- Based on exclusion
  - R/o infections, parasites, food, flea & contact allergy, primary seborrhea, MF, drug rxn
- Require THOROUGH history
  - Age of onset < 3 years of age, symptoms, seasonality
  - Glucocorticoid-responsive
  - Front feet affected
  - Affected pinnae
  - Indoor mostly



# A Word on Isoxazolines

- Inhibit Gaba-gated Chloride channels
- Prevents fleas, ticks and extra-label treatment for scabies
- Great way to perform a “maybe mite” trial when suspicious of scabies
- Break life cycle of fleas in suspected FAD

# What's New in Treatment?



- Goals

- Reduce & control pruritus → “Put the fire out!”
- Prevent subsequent allergen exposure and flare
- Restore barrier function of the skin
  - Treat secondary infections
  - Heal & rebuild protective function of skin

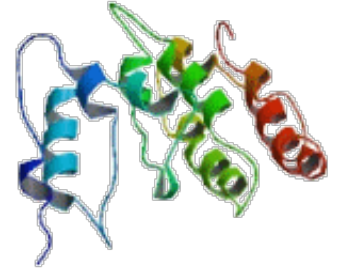


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# Antipruritic therapies

- Oclacitinib (Apoquel®) and Lokivetmab (Cytoint®) are newer, commonly-used therapies
  - Fast-acting
  - Offer symptomatic treatment for short-season atopy and for acute flares
  - Both target IL-3

# IL-31



- Pruritogenic cytokine produced by TH2 cells
- Serum levels correlates w/ AD severity in humans
- Injection into lab beagles induced transient pruritus
- Plays role in canine AD, but may not be major
- Found in 57% of dogs with naturally-occurring AD
  - Undetectable in normal dogs
  - Not found in skin biopsy of atopic dogs

# Oclacitinib

- Inhibits Janus-kinase 1 & 3, IL-2,4,6, 13, IL-31
- Use in dogs 12 months or older
- Rapid-onset
- Monitor for UTI, pyoderma, demodicosis and neoplasia, viral dz
- Occasional vomiting occurs
- Useful in performing initial work-up s/a parasitic control, diet trial



# Oclacitinib



- Beagles sensitized to IL-31
- Single dose of oclacitinib given orally versus placebo, prednisolone and dexamethasone
- Oclacitinib reduced pruritus in 80% of dogs 1-3 hours post dose compared to placebo
- Oclacitinib had faster onset of action than pred and dex and had greater inhibition of pruritus in first 12 hours

# Before and 1 month after Apoquel®



# Lokivetmab

- Caninized monoclonal Ab
- Binds, neutralizes IL-31
- Rapid, antipruritic effect
- No age restriction
- No liver or kidney metabolism
- Lasts 4-8 weeks in up to 80% of dogs



# Lokivetmab

- Pruritus improved in 87.8% of dogs in one 2018 retrospective study in 132 dogs
  - pVAS reduction of  $\geq 50\%$  in 77.0%
  - Dogs with severe pruritus & large or giant breeds had higher odds of improvement
  - Dogs w/ poor oclacitinib response less likely to respond to lokivetmab
  - Adverse effects: lethargy, vomiting, hyperexcitability, pain at injection site and urinary incontinence were reported in 11 of 132 dogs

# Topical Calcineurin Inhibitors

- CsA and tacrolimus ointment
- Localized AD
- Decrease symptoms in ~50% of patients after 1-3 months
- Mild irritation in first few days
- Practicality??
- 0.1% tacrolimus may be useful, safer than 0.3%
  - Nano-formulated CsA may be available



# Barrier Function Repair

- Topical PUFA's to restore
- Dermoscent® Essential 6® Spot on & Atop 7® products shown to reduce CS's, pruritus & TEWL
- Allerderm® spot-on improves lipid content skin, CS's but not pruritus



# Topical Barrier Fxn Repair

- Atobarrier Cream w/ Dermallay shampoo decreased CS's, TEWL, pruritus
- Douxo® Calm mousse ↓ inflammation
- Dechra® Atopivet line (2x/wk spot-on, collar, mousse)
  - Biosfeen® A sphingomyelin rich sphingolipid
    - maintains the epidermal barrier & inflammatory response
  - Dermial® Glycosaminoglycans (hyaluronic acid)
    - Hydration & skin renewal
  - Shown significant improvement in 4-8 wks

# Oral Barrier Function Repair

- Dermaquin® w/ hardy Kiwi ↓ inflammation w/ ceramides, linolenic acid, OFA's
  - Support skin hydration, decrease histamine release
  - Decreased CADESI scores combined with steroids & maintained low CADESI when stopped steroids



# Redonyl® Ultra

- Palmitoylethanolamide (PEA)
  - Bioactive lipid endocannabinoid-like
  - Inhibits chronic inflammation, pain and pruritus
  - Reduce pruritus in dogs with moderate AD
    - 160 dogs in open-label, multicenter study
    - 45% of dogs reached QoL values similar to normal dogs
  - 2017 study showed decrease in degranulating mast cells in tissue culture of ex vivo skin samples treated with cmpd 48/80



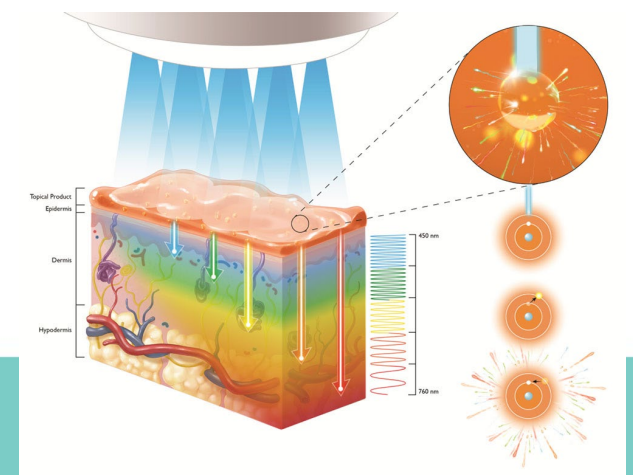
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# Consider Phovia

- **Photobiomodulation** → low-level light therapy that increases secretion of several GF's & collagen
- Accelerates natural skin regeneration & speeds wound healing
- Helps reduce use or duration of systemic ab's
- Use for surgical wounds, pyoderma, furunculosis, perianal fistula in dogs, cats, horses





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The background features a microscopic image of tissue, possibly showing cellular structures. A large teal triangle is overlaid on the right side of the image. In the bottom left corner, there is a solid orange triangle. The text 'DR. Joya' is written in a mix of black and orange fonts, with 'JOY' in black and 'A' in orange. Below this, the text 'DOCTOR OF VETERINARY MEDICINE' is written in teal, underlined.

DR.

Joya

DOCTOR OF VETERINARY MEDICINE

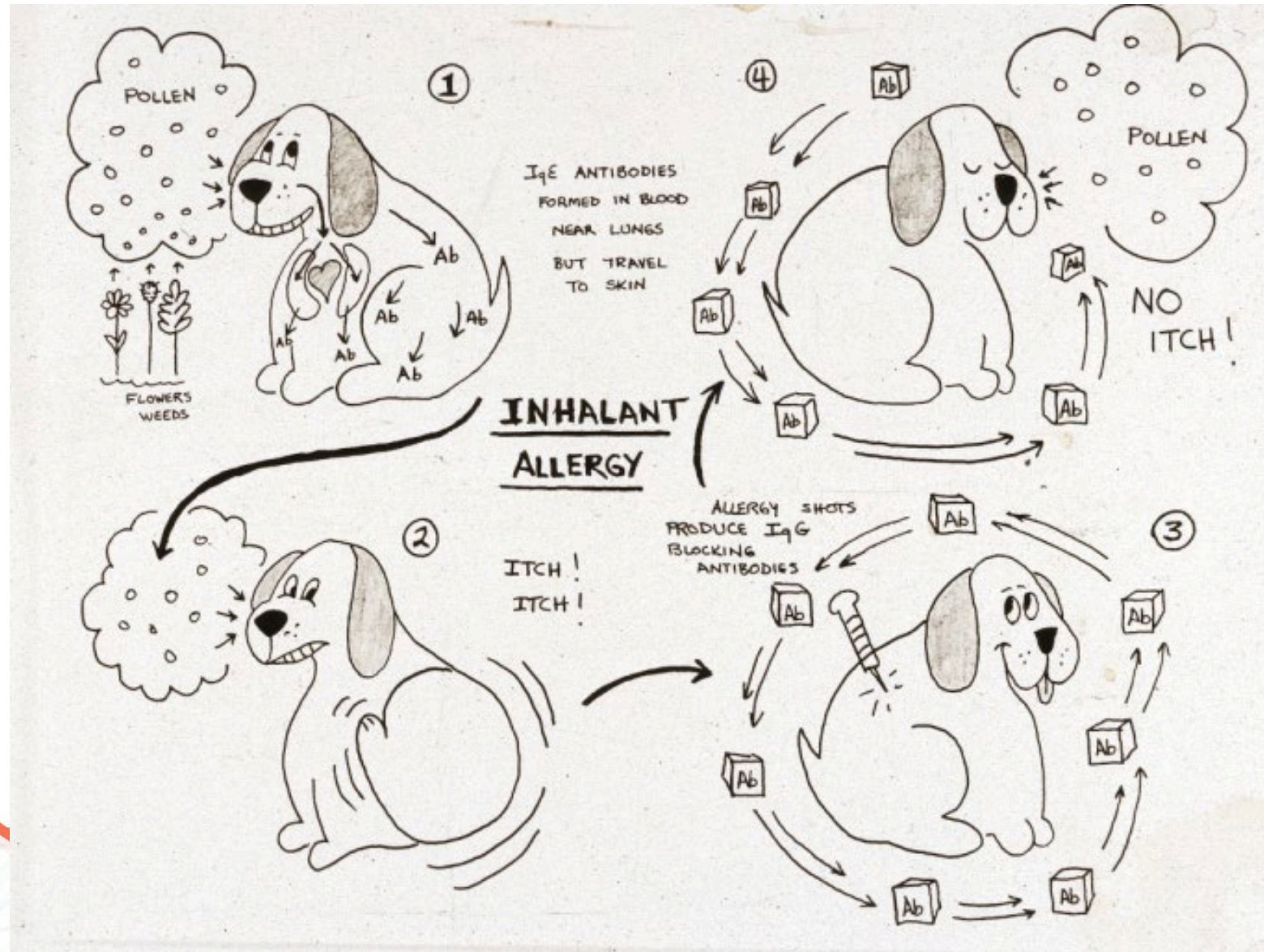
# Part 2: The Tried & True

# Allergen-specific Immunotherapy

- Only intervention to prevent development C'S & alter long-term course of disease
- Shift from Th2 to Th1 immune response
- 60-78% efficacy
  - can decrease amount & frequency of chronic therapy
- Individualized
- Safe → avoids drug side effects



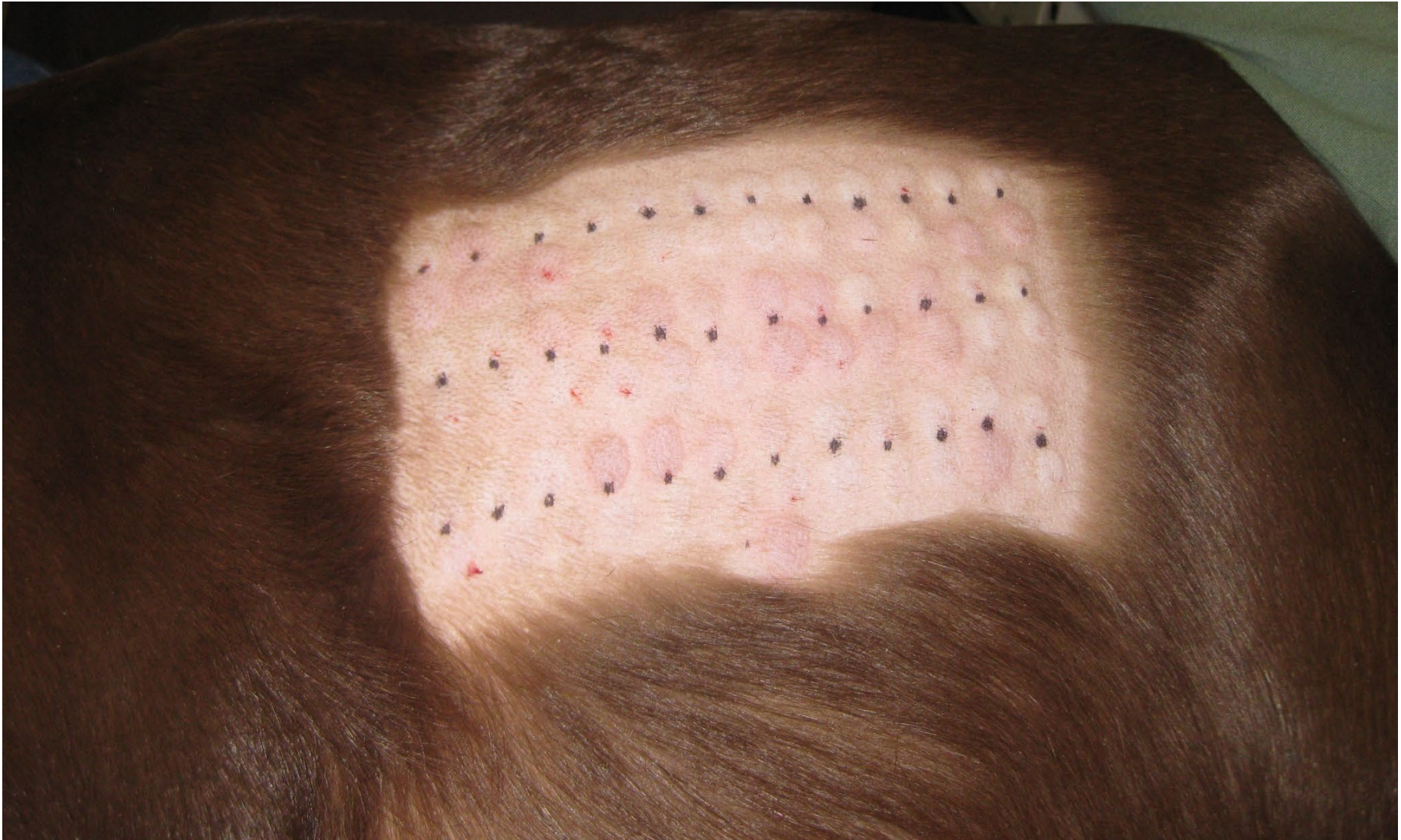
# Courtesy Dr. Gail Kunkle 1977



# ASIT

- May take up to 1 year for full efficacy
  - Must use anti-pruritic medications while initiating therapy
  - Adjust dose and frequency based on seasonal variations in pruritus and general severity
- Subcutaneous, sublingual & transdermal forms
  - Choose based on client preference, ability





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# Sublingual Immunotherapy

- Used in humans in past 50 years esp. in Europe
  - Safe, effective in reducing asthma & allergic rhinitis
  - Research shows efficacy in atopic humans & dogs
- Allergens absorbed under the tongue induce tolerance
  - Produce anti-inflammatory IL-10, T reg cells, increases IgA, IgG4
  - Effects may continue after cessation
- Local & transient oral pruritus may occur
- Very rare reports of anaphylaxis compared to SCIT
- Some improve within 6 months



# Regionally-Specific Immunotherapy (Respit®)

- Standardized formulation
  - based on 9 geographical regions
  - Oral or injectable
- Limited studies available on success



Injectable 10 ml  
multidose vials  
(10–20 week supply)

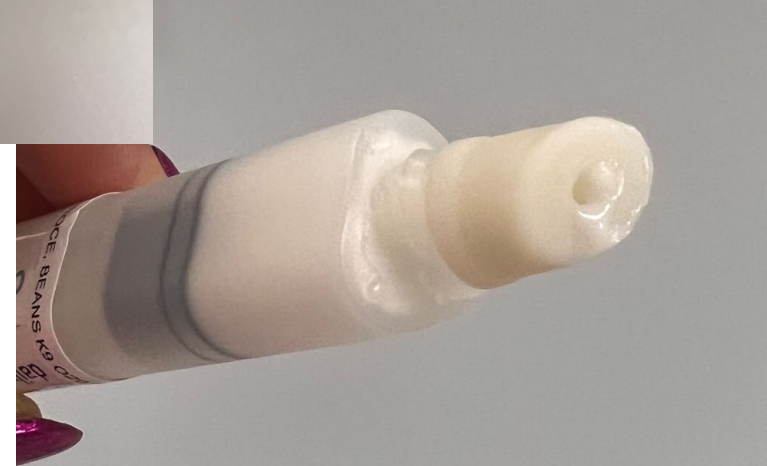
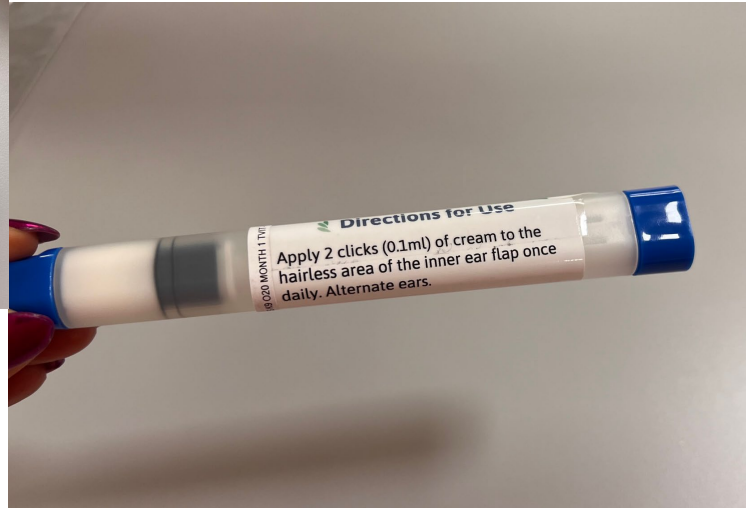


Oromucosal Spray 30 ml  
multidose bottles  
(14–21 week supply)

# Intralymphatic Immunotherapy

- Used in cat dander allergy & allergic rhinitis/conjunctivitis in humans
- Goals: shorter tx interval, less variability in AIT formulation, use less antigen, better compliance, avoid premature tx cessation & adverse rxns
- Long-term improvement after 3 monthly injections into inguinal lymph node under U/S guidance
- Few studies in dogs with inconclusive results
  - 0.2 mls alum precipitated allergen extract into popliteal L. node, monthly

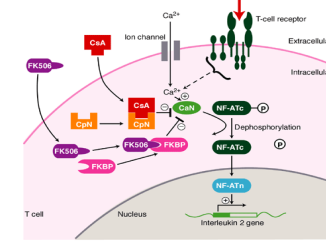
# Transdermal Immunotherapy



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# Cyclosporine

- Calcineurin inhibitor
  - May lead to sebaceous gland regeneration
  - Inhibits T helper and cytotoxic T cells, IL-2 & other inflammatory cytokines
- Humans: Anti-rejection drug, RA, Psoriasis, AD, alopecia, ulcerative colitis, IBS, Crohn's dz
  - Investigated in tx of asthma, brain injury
- Dogs & Cats: AD, lupus, vasculitis, IMHA, organ transplantation in cats
  - 78% effective in cats, liquid formulation

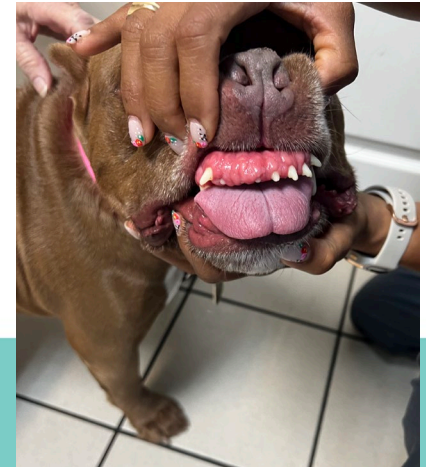


# Pharmacology

- Several formulations available
  - Sandimmune® ≠ Atopica®/Neoral®/Gengraf®
    - Doses are not bioequivalent btwn products!
  - Poorly bioavailable after oral dosing, decreased by presence of food
    - Emulsion achieves higher blood levels in dogs and cats
- Metabolized by liver via P450
- Excreted in the Bile

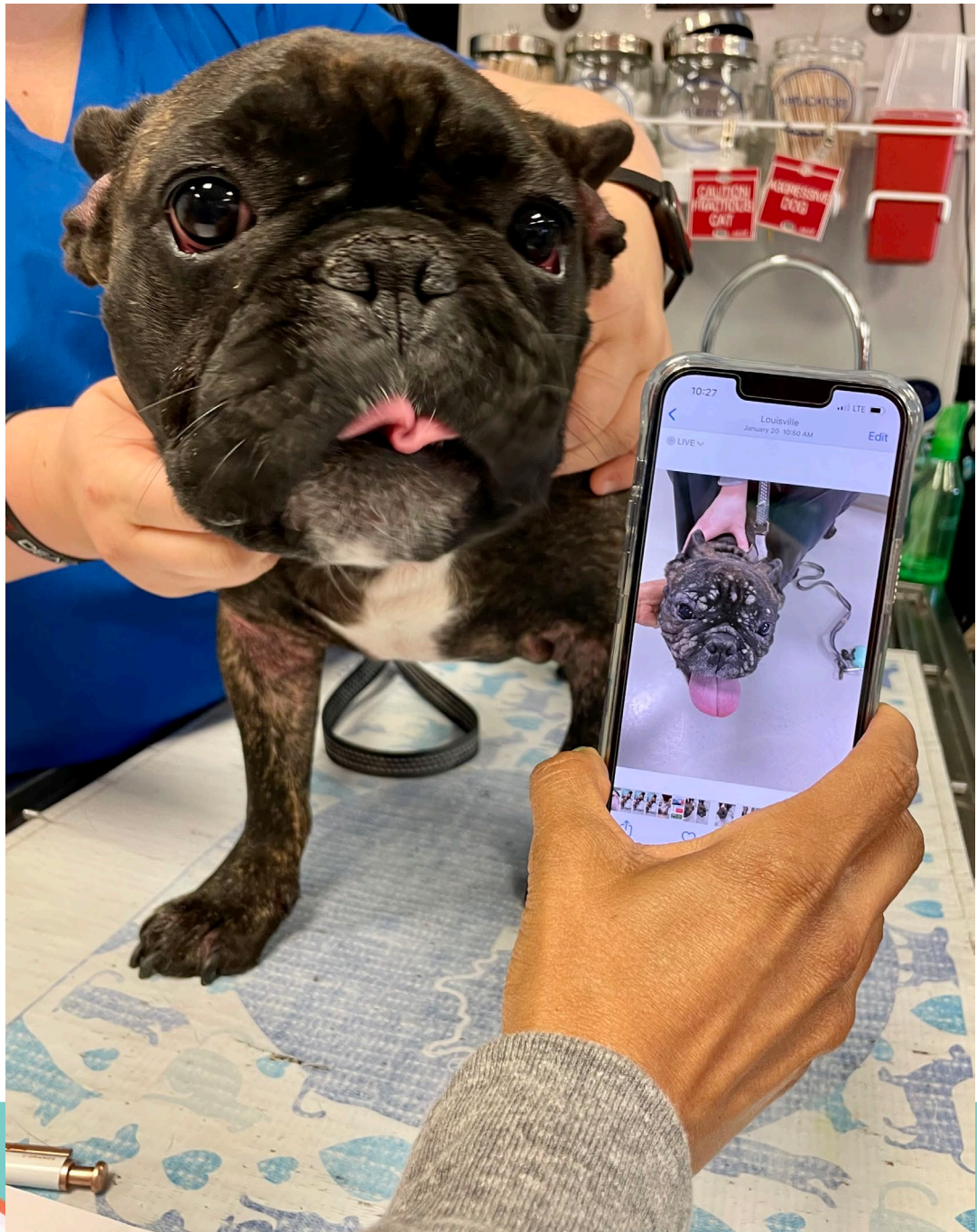
# Side Effects

- GI upset most common
- Use caution with renal, liver dz
  - Hepatotoxicity, nephrotoxicity at high blood levels
- Gingival hyperplasia, hypertrichosis, excessive shedding, papillomatosis
- Increased susceptibility to bacterial, fungal dz w/ prolonged use esp. in combination with steroids
- Can interfere with glucose metabolism
  - Use with caution in diabetic animals



# Psoriasiform Dermatitis

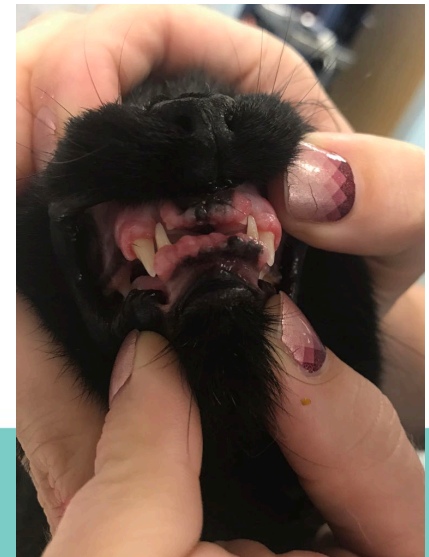




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# CsA Side Effects Continued

- In Cats
  - Fatal Toxoplasmosis in cats who become seropositive while on CsA; those seropositive prior do not repeat oocyst shedding at anti-inflammatory doses
  - Safest in indoor only cats → Avoid hunting, raw foods



B



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# One month after Atopica® & marbofloxacin



# Topical therapy

- Important to restore barrier fxn of skin
- Remove allergen exposure, irritation
- Decrease microbial overgrowth
- Fatty acid, lipid and ceramide containing can be helpful s/a
  - Allermyl® shampoo shown to reduce lesion scores and pruritus in 3-4 weeks
  - Douxo® Calm mousse with phytosphingosine, natural ceramide derivative
    - Decreases inflammation, but not TEWL

# Topical Therapy

- When & How to Use?
  - Recommend routine frequent bathing
    - Contact time is important!
    - Adjunctive wipes, spray or mousse can be helpful
  - Antimicrobial shampoos useful if infected, moisturizing if prone to dryness or anti-seborrheic if greasy or scaly
  - Ceramide and lipid containing useful for atopics



# Case Study: Sophie



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- 8-year-old FS Shorkie
- History of recurrent otitis since 2 years of age
- Pruritus and dermatitis at 5 years of age
- No response to Apoquel®
- Limited response to Depo injections
- Strict Z/D ultra diet trial with no improvement



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# Diagnostics

- Cytology
  - Ears- cocci and rods AU with yeast AS, Skin- nuclear streaming, 2-6 cocci per OIF ventrum
- CBC, chemistry and thyroid panel due to PU/PD, owners' concern for weight gain and diabetes, historical recurrent/nonresolving infection

# Treatment

- Infection control: Simplicef® for ear and presumptive middle ear infection w/ Surolan®, and prednisone to reduce stenosis & hyperplasia in the ears
- Barrier function restoration: Malaseb® baths
- Allergic Flare: Cytopoint® while beginning desensitization with ASIT
- Ectoparasite control: Treated with Bravecto® for possible scabies d/t high reactivity to dust mites on IDT & intense level of pruritus



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# Summary

- Canine AD is complex
- Multimodal approach tailored to specific patient
- Focus on controlling pruritus, reducing allergic flare and restoring skin's barrier fxn

# Any Questions?



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Disclaimer: Any misinformation, errors, or typos is attributed to these 3!

# Thank you!

For more ooey gooeys Watch "Pop Goes the Vet with Dr. Joya" on



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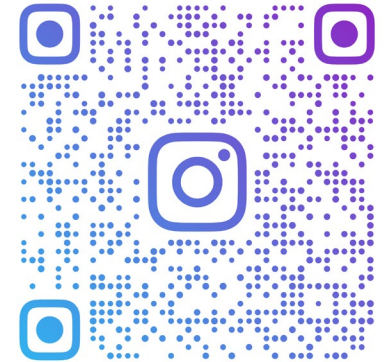
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