Canine Pruritic Skin Disease Part I and II: Understanding, Diagnosing, Managing Canine Atopic Dermatitis and Other Conditions

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Background/definitions

- Allergy/Allergic Disease : Immunologic response (hypersensitivity) to an allergen and mediated by cells or antibody (unusual biological response to stimulus → harmful/inappropriate effect)
- Atopy "strange disease" :Immunological response (hypersensitivity) to environmental substances ("allergens"): Three (IgE mediated) conditions in humans: Asthma—Hay Fever—Atopic Dermatitis ; +/- urticaria/hives, rhinoconjunctivitis, and gastrointestinal allergies
- Atopic Dermatitis: Genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies (otherwise; atopic-like dermatitis) most commonly directed against environmental allergens. (ACVD Task Force, 2001)

Historical perspective

- Canine Atopy: 1941: Canine atopy was first reported; "seasonal hay fever" (F.W. Wittich); 1960: Canine "allergic" conjunctivitis and pruritus reported (R. Patterson); Late 1960s to early 1980s numerous studies and reported cases of canine atopy; Canine "allergic inhalant dermatitis"(Wittich, Patterson, Halliwell- 1940s-1970s); 2000-present: Epidermal (skin) route of allergen challenge (percutaneous)-Clinical observations, Histological evidence, & Experimental models
- Cyclosporine: 1970-1972: B. Thiele (soil samples): (1) Wisconsin, USA and (2) Hardanger Vidda in Norway; from the fungus Tolypocladium inflatum (Beauveria nivea); 1974-1976: Selective immunoregulation of T cells without excessive toxicity (J.F. Borel and others); "Interesting Compound"; 1983: Sandimmune® (cyclosporine USP)- FDA approved, prevent graft rejection in transplantation (i.e., kidney transplantation); 1987: Human atopic dermatitis (von Joost et al.); 1995: Neoral® (cyclosporine USP, modified; microemulsion) FDA approval (less dependeant on bile); 2001: Canine atopic dermatitis (Fontaine and Olivry); 2003: Atopica® (cyclosporine USP, modified; microemulsion) FDA approval for dogs (atopy)

Basic immunology

- Numerous cells involved: (1)Langerhan's Cells (antigen presenting cells)- IgE attached → stimulate local T-cells → cytokines; Antigen attached → mast cells → degranulate → histamine; (2) T-cells (Lymphocytes)-Activated→ release inflammatory mediators; (3) Mast Cells (and Basophils)-Degranulation and histamine release; Role in canine atopy is controversial; (4) Keratinocytes (skin cells)- Produce inflammatory mediators (chemokines/TARC); Prime/attract T-cells; Pollen → Skin Cells (keratinocytes) → chemokines releases (TARC); → Attract to receptors on T-cells → Cytokines (IL-4) → itching, swelling, and redness (attracts other cells); (5) Eosinophils-Degranulation and histamine release
- Immunoglobulins (Proteins)- produced by B-cells: IgE & IgGd- IgE (Immunoglobulin E)- Antibody (protein); part of immune system, Produced by plasma cells/B-cells (another lymphocyte), Protect the animal against invading parasites, Responsible for typical allergic reactions, IgE specifically recognize an allergen/protein (e.g., pollen), IgE Receptor binds to allergen, Portion of IgE interacts with cells (mast cells, eosinophils, Langerhan's cells, keratinocytes, etc.); "primes" (gets them ready) these cells for release of substances (e.g., histamine) associated with allergy symptoms, Re-Exposure: Allergen → allergy response → degranulation (seratonin, heparin, histamine, cytokines) → perpetuate the response
- Helper T-cells: Altered helper T-cell (lymphocyte) response: Release of inflammatory mediators (cytokines)- TH2 Response (early): IL-3, IL-4, IL-5, IL-6; TH1 Response (later): IL-2, IFNα, etc. and "Help" B-cells/plasma cells produce antibodies (e.g., IgE), promote growth and differentiation of B-cells.
- Pathogenesis
    - ❖ Pollen→ Skin → Bind to IgE located on Mast Cells → Degranulation →Histamine and other mediators → influx of inflammatory cells (eosinophils) → release more mediators (Results: itching, swelling, and redness)
    - ❖ Pollen → Skin → Bind to IgE located on Langerhan's Cells→ Pollen now "presented" to the T-cell (in lymph nodes)→ Cytokines (IL-4, IL-5)‡ → itching, swelling, and redness (attracts other cells) & leads to "memory" for next time there is exposure ("sensitization")
- Hereditary, mode of inheritance is unknown, Strong breed predilection (Labrador Retriever, Golden Retriever, Soft-Coated Wheaton Terrier, West Highland White Terrier, Jack Russell Terrier, Bulldog, Boston Terrier, Boxer, Pit Bull, Shar Pei, Shih Tzu, Weimaraner); Marked familial involvement: Studies have shown: ~ 60% of offspring will develop atopy if both parents affected; 10 -15% of the canine population are atopic; Seasonality (40-75%); Most progress to all year; Age-6 months - 3 years old (70% 1-3 years); No gender predilection
- Common allergens: House Dust Mites +/- Storage Mites; House Dust, Feathers, Wool, Kapok, Dander, Grasses, Weeds, Trees, Insects; Atopy is the usually regarded as the second most common cause of pruritus (itching) in dogs-Flea Allergy Dermatitis (FAD) is the still thought to be the most common cause of pruritus in dogs (not all allergic); It is suggested that at least 75% of atopic dogs also have FAD; Some may also be food allergic (cutaneous adverse food reaction)
- Presenting Clinical Signs: Itching (pruritus- hallmark feature; #2 cause of pruritus as fleas still seem to be the #1 cause; but about 75% of atopic dogs are also flea allergic); Bacterial Pyoderma (recurrent) & Malassezia Dermatitis (yeast); Ear Infections/Itchy Ears (otitis);

Tearing/Red Eyes (conjunctivitis); Flaky Skin/Scaling (seborrhea); Sweating (hyperhidrosis); Hair Loss (alopecia) & Hot Spots; Smelly Skin (malodorous); Anal Sacculitis- almost 30%; Rhinitis and Sneezing;

- Body sites most affected: Feet (interdigital/claw fold); Ears; Face (lips, chin, muzzle, around the eyes); Belly (ventrum); Neck; Armpit (axillae); Groin (inguinal Region); Distal Limbs (carpal/tarsal/digit); Flanks (sides); Chest; Flexural Regions (elbows and hocks); Back (dorsolumbosacral); Perivulvar and Perianal
- Common skin lesions: Bacterial Pyoderma (surface-superficial-deep)-Papules, pustules, scaling (Seborrhea), Lusterless hair coat (Dull), Circular crusted papules (Collarettes) ; Ear Disease-Dark Waxy and Malodorous Ears; Itching-Associated: Hair Loss (Alopecia), Red Skin (Erythema), Thick Skin (Lichenification), Self-Trauma/Scratches (Excoriations), Dark Pigmented Skin (Hyperpigmetation), Red-Brown "salivary staining", Other: Hives (Wheals/Urticaria), Hot Spots (Acute Moist Derrmatitis), Lick Granulomas (Acral Lick Dermatitis), Pyotraumatic Folliculitis & Furunculosis , Interdigital Folliculitis & Furunculosis
- Urticaria (multiple hives or wheals): Nodular disease- transient focal swellings (dermal edema) on the skin or mucous membranes +/- pruritus +/- discomfort; Mast cells +/- basophils- release substances (degranulation) → swelling and inflammation → vasodlation → spill-over of fluids into the skin; Breeds Predisposed: Boxers, Bulldogs, Pit Bulls (especially white-coated dogs); Tufted papules; Etiology: Immunological causes (hypersensitivity)-offending protein/material (antigen) reaches the systemic circulation (injection, ingestion infection, inhalation, per-cutaneous penetration; Contactants (cosmetics, plastic, collars, shampoo, blankets, bedding, and more); Non-immunologic causes include physical causes -(dermatographism, temperature/thermal extremes, exercise induced, stress, light/sun-light exposure, immune-mediated skin disease (EM, PF), "secondary" urticaria (infections including ringworm, vascular disease, cancer, psychological, etc.); Idiopathic; Clinical Signs: Wheals- usually round (2mm to 10cm)-conventional (2–3 mm to 3–5 cm); papular (uniform/small, 3–6 mm), & giant (single or multiple large wheals, up to 20–40 cm); Lesion Classification: (a) typical - normal skin surface aside from the raised lesions; (b) oozing (transudative/exudative) - severe edema in the upper dermis leads to fluid (serum) leaking to the surface of the skin causing a matted/crusted appearance of the hair coat; (c) gyrate or polycyclic urticaria- mimic (EM), drug reactions are most likely ; (d) angioedema- subcutaneous tissue involved
- Acral lick dermatitis (ALD): Background-Self-induced dermatological condition, Secondary to compulsive/excessive and chronic licking in one or more areas, ~70% have concurrent fear- and/or anxiety-based conditions (e.g., separation anxiety, noise phobia, anxiety-related aggression), Constant licking prevents the area from healing; Etiology- Multifactorial-Allergic Dermatitis (atopy, cutaneous adverse food reaction, or fleas), Orthopedic Disease/Osteopathy (arthritis, joint disease, bone pain, other), Neoplasia, Infections (Bacterial +/- Fungal/Yeast), Foreign Body (e.g., grass awn, wood splinter, etc.), Ectoparasites (sarcoptes and demodex mites), Psychogenic/Compulsive Behavior, Neuropathy, Trauma (laceration), Metabolic (hypothyroidism vs. Cushing's disease), Idiopathic; clinical signs-Firm (fibrotic), raised, hairless areas of skin that may be hyperpigmented (darkened with pigment) or even erythematous (red), due to the chronic licking of the area, Center of the lesion often has a "scooped-out" appearance that is ulcerated/erosive, red, and moist, or may be covered by a scab (serous crust), Extremities (usually); management- Manage the underlying cause, Address secondary infection (Appropriate Antibiotic Choice, Dose, Frequency), Corticosteroids, Behavior Modifying Medications, Topical Treatments and/or Topical Deterrents, Narcotic or Opioid Receptor Antagonists, Mechanical Blocking Device, Laser Surgery
- Pruritus: Degree is variable (1-10 scale), Influenced by: weather factors (temperature & humidity); individual factors (stress/anxiety); allergen levels; coexistent allergies; infections; ectoparasites (fleas/mites); metabolic disease (Cushing's disease) etc. (allergic threshold)
- Diagnosis: Proposed Clinical Criteria: Prelaud et al, 1998, Willemse, 1986 & 1988, Scott, Miller, and Craig, 2000-Summary of Some Common Criteria: Corticosteroid-responsive pruritus, Red feet and ear flaps & lip swelling (chelitis), 1st signs between 6 months to 3 years of age, Relapsing dermatitis and/or otitis (bacterial/yeast), Exacerbation upon contact with causative agents—e.g., vegetation (grass/weed)
- Diagnosis: Proposed Clinical Criteria
    - Prelaud *et al*, 1998

Major criteria (3 of 5)
1. Corticosteroid-sensative/responsive pruritus
2. Red ear flaps (Erythema of the pinnae)
3. Red front feet (Erythematous pododermatitis)
4. Lip Swelling/Dermatitis (Chelitis)
5. Appearance of 1st signs between 6 months to 3 years criteria

    - Willemse, 1986 & 1988

Major criteria (3 of the following)
1. Pruritus
2. Typical Morphology & Distribution: facial and/or digital involvement or lichenification of the flexor surface of the tarsal joint and/or the extensor surface of the carpal joint
3. Chronic or chronic relapsing dermatitis [AD]
4. Individual family history of atopy, and/or breed predisposition
AND (must)

Minor criteria (3 of the following)

1. Onset of symptoms prior to 3 yrs
2. Facial erythema & chelitis
3. Bacterial conjunctivitis
4. Superficial staphylococcal pyoderma
5. Hyperhidrosis
6. Immediate positive intradermal test to inhalants
7. Increased serum allergen-specific IgE
8. Increased serum allergen-specific IgGd

- Scott, Miller, and Craig, 2000

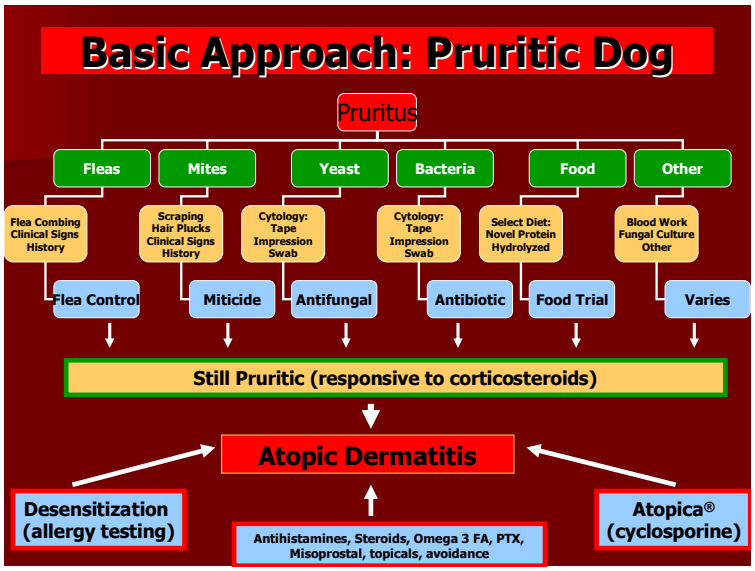
Major criteria

1. Bilateral Lesions of the plantar surface of the interdigital spaces of the front paws
2. Onset of signs between 6 months to 3 years
3. Peribuccal erythema or erythema of the medial surface of the pinnae
4. Anitis (anal fissures)
5. Recurrent dermatitis for > 2 years

Minor criteria

1. Family history
2. Exacerbation when the dog contacts vegetation (grass/weed)
3. Rhinitis
4. History of urticaria/angioedema
5. Acral lick dermatitis
6. Hyperhydrosis
7. Lichenification of the fold of the hock and/or the cranial surface of the carpus

Basic approach: Pruritic dog



- Cytology, Scraping, and Combing: Ear Cytology Swabs; Skin Cytology (yeast and bacteria) Tape (Scotch® 3M Packing Tape), Impression, Swabs, Clawbed Scraping, Skin Scraping (scabies, demicosis, cheyletiellosis, etc.), Hair Plucks, Flea Combing, Cytology: Nailbed Scraping-Look for yeast and bacteria, Use a spatula or a cotton tip applicator broken in half using the split end for "scraping" the material; Diff-Quik® and/or Gram Stain
- Antibiotics and Anti-fungal (topical and/or oral)- May need to consider culture of skin and/or ears: look for MRSA, MRSP, MRSS, MDR; Technique: Sterile Swab Tissue- Pustule, Epidermal Collarette (margins), Serous Crust (underneath)Draining Tract, etc.
- Food and Other-Diet /Food Trial; Wood's Lamp, KOH Preparation, Fungal Culture; Bloodwork, Biopsy, Culture & Sensitivity; Dermatophytosis
- Fleas (Flea Allergy Dermatitis)
    - Fleas are wingless arthropods that feed on/infest the hair coats of mammals and the plumage of birds. There are over 2,200 species and subspecies distributed worldwide, with at least 95% known to parasitize mammals; History of about 60 million years (found on pre-historic mammals); Fleas are the most common external parasite of companion animals. Fleas are complete metamorphic insects, having developmental stages consisting of eggs, larvae, pupae, and adults (1-5mm); Flea allergy dermatitis (FAD) is the most common skin disease of cats and dogs. The underlying cause is a hypersensitivity to the

saliva of fleas (Flea Bite Hypersensitivity); In several regions of the U.S.A and worldwide, FAD is the most common canine disease!; Aside from FAD, fleas can cause iron deficiency anemia/blood loss (young animals), tissue/hide damage, peripheral eosinophilia, serve as intermediate hosts (i.e. Dipylidium caninum-fleas harbor cysticercoids), and serve as vectors for several disease agents (some are zoonotic/public health concern) and a clinically insignificant filarial parasite (Dipetalonema reconditum); In geographic regions where there are no fleas (low humidity and/or high elevations (>5,000 ft) e.g., Denver, Lake Tahoe, Las Vegas, etc.), atopic dermatitis (AD) is the most common skin disease of canine dermatologic patients; Developmental cycle includes egg, larva, pupa, and adult stages. The metamorphosis is complete (holometabolous); Variable length of the cycle (12 - 190+ days) depending upon environmental conditions; Under conditions of 75□F and 78% relative humidity, the developmental cycle usually varies from 16 to 26 days depending on the insect's gender. The average is 21 days; At low altitudes and ideal temperature and humidity, the developmental cycle has taken as little as 12 days; Dryness and high heat, very high humidity concurrent with high temperature, very wet conditions (drowns the larvae), or extreme cold is not good for the fleas, prolonging the life cycle and thus being deleterious to larvae; Flea infestations usually originate from the environment and not from specific contact with an infested/carrier host. This is important in the prevention of flea-related disease/conditions; Cenocephalides felis felis (Cat Flea)- #1 flea infesting BOTH (97%) cats and (92%) dogs. Readily attack humans and/or other mammals if desired host is absent. Cat fleas are known to infest >50 different hosts worldwide. Aside from canines and felines, in North America, the other commonly infested animals include raccoons, opossums, ferrets, etc. Moves freely through the hair coat. Intermediate Host: Diplydium caninum; Clinical Signs: Scratching, chewing, licking, and biting; About 60% of flea allergic dogs develop clinical signs between 1 and 3 years of age; Papules, serous crusts, salivary stains (from licking), excoriations (self-trauma), scaling, and erythema; Common anatomical distribution of the lesions are in the back half of the body near the lower back/tail (dorsal lumbosacral region), inside the back legs (caudal medial thighs), tail head, belly (ventral abdomen), and around the belly button region (umbilicus/umbilical fold); It is rare for the ears and feet to be involved; Many of the areas described become alopecic, lichenified, and hyperpigmented; Secondary bacterial and yeast infections.

- Diagnosis: Direct observation of fleas and flea excrement (flea dirt) is helpful; aggressive flea combing; Very common to not see any fleas during the exam; "Spot test" - Collect suspected flea feces (comma shaped) on white paper, add water, and one may observe red staining of the paper, which is re-hydrated blood or “flea dirt.” Other diagnostics available include skin testing (saline-histamine-flea saliva), blood testing (Allercept® -Heska Corp.), and biopsies. None of these tests are usually necessary.
- Treatments: Minimizing the pruritus; Treat secondary infections caused by the excessive scratching, chewing, and licking; Eliminate the flea population and to prevent fleas from biting in the future; target all stages of life cycle (adults are only 5% of the population). Some Products: Program® and Sentinel® (lufenuron); Nylar® (pyriproxifen); Frontline Plus® (methoprene); Advantage® (imidacloprid), K9 Advantix® (permethrin), Advantage Multi® (moxidectin); Frontline® Spray, Frontline Plus® and Frontline Top Spot® (fipronil); Revolution® (selamectin); Capstar® (nitenpyram); Comfortis®(spinosad); Promeris® (metaflumizone/amitraz); Vectra 3D® (dinotefuran, permethrin, pyriproxifen); see appendix i for flea therapy choices.

Mites (Brief overview)

- Demodectic mange
  - Background: Demodicosis is a common skin disease encountered in veterinary practice (Sischo et al., 1989 and Miller et al, 2001), Usually associated with the over-proliferation of the mite Demodex canis (localized and generalized form), Normal inhabitant of the hair follicle (low numbers due to immune system), sebaceous glands, and sweat glands (Nutting et al., 1978; Shipstone 2000; Scott et al. 2001), Dam → pups "direct contact" 2-3 days of life (post-natal period), not later; transmission occurs from bitch to neonates while nursing during first 2-3 days of life (Miller et al 2001; Gaafer and Greeve, 1966), Secondary bacterial folliculitis is common , Not believed to be contagious to other animals or to humans; NOT survive in the environment, not zoonotic, Lack a terminal anus (not excrete fecal matter or intestinal proteins), thus no IgE-hypersensitivity reaction/pruritus, Pruritus is secondary to bacterial infections. Etiology: Immunosuppressed (young, old, pregnant, chemotherapy, metabolic disease, diabetic, corticosteroids, etc.); Forms/Categories: Localized Form and Generalized Form and Juvenile and Adult Onset; Species: Demodex canis (Most prevalent, present in hair follicle and rarely the sebaceous glands. This is referred to as ‘red mange.’); Demodex injai (Desch et al., 2003, Mueller and Bettenay, 1999) (Large-bodied (all life stages greater in size as compared to D. canis). Present more commonly in sebaceous glands. Associated with dorsal seborrheic dermatitis (Bensignor et al., 2006 and Hillier et al., 2002) as well as intense facial pruritus (Forsythe et al., 2009)); Demodex cornei (Present in the stratum corneum (surface). This is about half the side of D. canis (Tater and Petterson, 2008, Chesney, 1999, Tamura et al., 2001, Chen 1995, Mason, 1993)); Clinical Signs: Demodex canis: alopecia, scaling, follicular casting, papules, pustules, folliculitis/furunculosis (mites present in follicles), and comedones (often non-pruritic), crusting, epidermal collarettes, erythema, swelling, discomfort, hyperpigmentation, lichenification, lymph node enlargement, secondary pyoderma (pruritus), ceruminous otitis (sometimes just ears)- short coated breed predisposed (e.g., Bulldog, Boxer, Pit Bull, etc.) (Brockis, 1994; Knottenbelt, 1994), Demodex injai: dorsal greasy seborrheic dermatitis (seborrhea oleosa) as well as intense facial pruritus, secondary pyoderma-e.g., WHWT, Shih Tzu, Yorkshire Terrier, Wirehaired Fox

Terrier, etc.; Demodex cornei: often detected with the aforementioned mite populations, thus similar clinical signs, more often associated with pruritus, secondary pyoderma; Treatment: Ivermectin (PO at a dosage of 0.25mg/kg daily for 7 days, the 0.5 mg/kg daily for 3-6 or more months (until 60 days of completely negative scrapings); bathe with benzyl peroxide-based shampoo; beware of the herding breeds (Collies, Shetland Sheepdogs, Border Collies, Australian Shepherds, Old English Sheepdogs) who have homozygous mutations in their MDR1 (ABCB1) genes (abnormal P-glycoprotein proteins pumps in blood brain barrier) allowing the ivermectin to penetrate/remain in the central nervous system; cheek swab of DNA to the College of Veterinary Medicine Washington State University (www.vetmed.wsu.edu/vpl.); beware of other medications blocking P-glycoprotein pumps (e.g., ketoconazole, author does not use this with ivermectin) or medications that are substrates (e.g., cyclosporine, author still uses this with ivermectin); "White feet, don't treat!"; Doramectin (Dectomax®): reported that 0.6mg.kg weekly is effective (unlike ivermectin, needed daily), avermectin; treatment and control of internal and external parasites of cattle; Milbemycin oxime (Interceptor®): 0.5 to 2 mg/kg every day for 3-6 or more months (until 60 days of completely negative scrapings); wider safety margin than ivermectin, with similar side-effects (stupor, tremble, ataxia; vomiting) when using higher doses/do not exceed 2.5mg/day; give with food; usually safe in collies or other dogs with the MDR1 (ABCB1) gene anomaly; expense is a limiting factor; Moxidectin (Cydectin®): 0.4 mg/kg/day; step-up dose gradually; milbemycin; similar side effects as ivermectin; Imidicloprod + moxidectin (Advantage Multi®)- moxidectin is a milbemycin and probably using this topically every 2 weeks for a minimum of 3 treatments would be effective (controversial); likely require longer course of treatment; Amitraz (Mitaban®)- monamine oxidase inhibitor (MAOI) (never use with hydroxyzine, certain tricyclic antidepressants (amitriptyline, doxepin), and antihypertensive medications) and avoid in owners taking MAOIs such as selegiline (Parkinson's disease treatment), as contact with amitraz could result in an overdose of MAOIs, which could lead to serotonin syndrome (myclonus, autonomic dysfunction and an altered mental status); alpha 2 agonist; prostaglandin synthesis inhibitor; transient sedation may be seen, as well as, edema, erythema, pruritus, anorexia, or PP, PU, PD, bloat, vomiting, diarrhea, ataxia, convulsions, personality changes, hypothermia, urinary incontinence, transient hyperglycemia, glucosuria, bradycardia, and even death; FDA licensed (only FDA approved treatment for demodex) use is 250 ppm (1 vial/2 gallons water) every 2 weeks (for 3-6 or more months (until 60 days of completely negative scrapings); drug works better at greater concentrations (off-label use up to 500 ppm (1 vial/1 gallon) and frequency; relapses occur in 10% of cases; never use in Chihuahuas and in pregnant and lactating bitches and in puppies less than 12 weeks of age; if severe: weak, ataxia, bradycardia, use alpha 2 antagonist (e.g., yohimbine (0.11 mg/kg IV; use pre-dip in future) or antipamezole (Antsedan®); pre-bath: benzyl peroxide shampoo (follicular flush, degrease, crust removal, kills bacteria); this is a dip—do not rinse after application; Metaflumazone + Amitraz (Promeris®)- using this topically every 2 weeks (until 60 days of completely negative scrapings) shows promise, risk PF-like reactions

Cheyletiella mange

- Cheyletiellosis: Cheyletiella yasguri, Cheyletiellidae, Non-Burrowing (rapid movement in pseudotunnels); pierce skin with chelicerae, Entire cycle on host (14-21 days), Adult can live up to 10 days off the host, contagious, zoonotic, cats, rabbit, dogs, clinical signs- mild scaling dermatitis ("Walking dandruff"); dorsal distribution +/- miliary dermatitis (papular-crusting), erythema; alopecia (ventral); pruritus (hypersensitivity)- variable degree; Diagnosis (40% chance of finding mite)-clinical signs, superficial skin scrapings (large mites), combing, acetate tape preparations, fecal flotation (eggs), biopsy; Treatment: Selamectin (Revolution®) Topical q 2 weeks for 3 doses, Lime Sulfur 2.5% (weekly; 6-8 dips), Fipronil (Frontline®-2 applications 0.25% spray or 10% topical q 30 days), Ivermectin 1% 0.2-0.5 mg/kg SQ q 2 weeks for 3 doses or 0.5% "pour-on" q 2 weeks for 2 months

Sarcoptic mange

- Sarcoptes scabiei var. canis; mites burrow in the top layer of skin and form little pockets for breeding; the mites tend to be specific to certain species, but can be transiently transferred to other animals, including humans. However, these mites do not spend much time on people and the main problem is the risk of a hypersensitivity to the mite; Sarcoptic mange is a very pruritic condition (clinical signs beginning 1-2 weeks after initial exposure). If untreated, adult mites multiply causing severe itching; Obvious skin lesions will become visible within 30 days of initial exposure; All in contact susceptible animals are usually treated to avoid re-infestation; The mites are unable to survive for long periods of time off the host; In ideal conditions, (lower temperatures and high humidity) female mites can live up to 21 days (average survival time is usually 4-6 days); Animals most at risk for contracting scabies have lifestyles that involve exposure to multiple other animals; Shelters, boarding kennels, doggie day cares, dog parks, and grooming parlors are usually incriminated. Animals that have contact with wildlife such as foxes, squirrels, and coyotes are also at an increased risk.
- Clinical signs: Unremitting pruritus (scratching, licking, chewing); Location of Lesions: elbows, hocks and edges of the earflaps (ear margins) in dogs; prefer sparsely haired areas; Usually, an erythematous rash may be evident over the chest, abdomen, hocks, axillary region, face, and other regions; As the condition progresses, thick, yellow adherent crusts may develop at the aforementioned affected areas; The condition is progressive, if left untreated, and will have a minimal response to traditional anti-itch therapies (corticosteroids, cyclosporine, anti-histamines)
- Diagnosis: Sarcoptic mange in is diagnosed by either microscopic examination of a skin scraping, or response to appropriate therapy; The mites can be very difficult to find on skin scraping (scabies incognito). They are only visualized 30% - 50% of the time. Finding just one 1 mite, mite egg, or mite fecal material is diagnostic; Often, if the clinical signs are suggestive of Sarcoptic mange, a

therapeutic trial is recommended to "rule out" this disease; Sometimes chronic cases become very crusty and have large numbers of mites (Norwegian Scabies- an increasing concern in immunocompromised humans).

- Treatment (current): Treat all in contact animals; if you suspect→ treat
- Ivermectin (PO or SQ at a dosage of 500 micrograms/kg q 3-7 days for 3-4 weeks- (once every 2 weeks for 3 treatments SQ is likely adequate)
- Selamectin (Revolution®) (apply ½ of the tube directly to the skin between the shoulder blades and the other half directly to the skin on the rump), do NOT bathe between applications (just 24-48 hours before the next application is due); every 2 weeks for 3 treatments
- Milbemycin oxime (Interceptor®): 2 mg/kg every other day for 8 treatments (98% effective); weekly for 3-5 treatments (71-100% effective)
    - Imidicloprod + moxidectin (Advantage Multi®)- moxidectin is a milbemycin and probably using this topically every 2 weeks for 3 treatments would be effective
    - Lime Sulfur: weekly dips; 6-8 weeks (can use as an adjunctive therapy)
    - Amitraz (Mitaban®) at 0.025 to 0.05%: sponge-on; applied for at least 3 doses (weekly or biweekly intervals); NOTE: Problematic/toxic for diabetic pets and diabetic owners; deadly for Chihuahuas; not to be used for puppies less than 3 months of age and nursing bitches. Secondary effects: changes in blood glucose, lethargy, depression, bradycardia, salivation, etc. (reversal agent: yohimbine); Also, use of a Preventick® collar has NOT been shown to effective at treating an active mite infestation, but may prevent a problem
    - Fipronil (Frontline®): not the best choice, but at 0.25% it has been anecdotally reported as effective when used as a sponge-on (spray formulation) at a dose of 3-6 ml/kg (2-3 treatments at weekly intervals), may be good for very debilitated or young animals

Bacterial infections

- **(**4) main reasons why pyoderma is more common in dogs as compared to other mammalian species: (1) thin, compact stratum corneum; (2) relative lack of intercellular lipids in the stratum corneum; (3) lack of a lipid-squamous epithelial plug in the (ostia) entrance of canine hair follicles; and (4) relatively high (basic) pH of the skin.
- (3) main types of bacterial infections: (1) Surface Bacterial Infections- just epithelium involved; (2) Superficicial Bacterial Infections (Superficial Pyoderma)- epidermis & follicular epithelium; and (3) Deep Bacterial Infections (Deep Pyoderma)- deeper than hair follicle, epidermis, follicular epithelium, & deeper than hair follicle→ breaks thru follicular wall → furunculosis & infection of dermis/SQ/cellulites/panniculitis
- Predispositions
    - Skin immunocompetence (e.g., allergies); #1 cause of pyoderma
    - Systemic immunoincompetence (e.g., metabolic disease)
    - Severe follicular damage (e.g., demodex, scratching)
    - Severe dermal damage (e.g., demodex, scratching, fleas, scabies)
    - Trauma (i.e. pressure, licking, chewing, scratching, etc.)
    - Inappropriate treatment for superficial dermatitis (e.g., inappropriate choice, duration, and/or dose)
- Pyoderma pointers
    - Treat the bacterial pyoderma for a minimum of 3-4 weeks.
    - Make an appropriate choice (see chart in the appendix).
    - Treat for 7 days past clinical cure (may take longer in deeper pyoderma).
    - If no response to antibiotic, there may be resistance, inadequate dose, wrong frequency, poor owner compliance, or maybe another disease (e.g., pemphigus, fungal, ectoparasites, etc.).
    - Do not use a lower dose to save the client money, they end-up spending more because the infection does not resolve. Also, inadequate dosing promotes resistance.
    - Do not hesitate to culture the skin (e.g., pustule, epidermal collarettes)- swabs and/or biopsy sample for culture. There is a very noticeable increase in resistance.
    - Staphylococcus pseudintermedius is still the most prevent, but more concerning species are on the rise: Staphylococcus hemolyticus & Staphylococus schleiferi etc. (Methicillin and Oxacillin resistant infections are increasing.)
        - Coagulase positive, relatively heat resistant, relatively tolerant to antiseptics (as compared to vegetative forms of most bacteria), resist dehydration
        - Virulence factors: e.g., protein A, toxic shock protein, hemolysins, enterotoxins (A, B, C, D), Lipoteichoic acid, coagulase, peptidoglycan - most promote adhesion to epithelial cells
        - Protein A & enterotoxin c- upregulate adhesion molecules on keratinocytes, act as super-antigens (strong T-cell activation) to ↑the local cutaneous and immunological response
        - Some strains produce a slime layer that encapsulates the bacterium- Inhibits ability to be phagocytized and helps in adherence.
        - Lipoteichoic acid and protein A- most important adhesion molecules, bind to surface receptors (fibronectin , vitronectin)

- The days of "cephalexin fixes everything" are slowly going away!
- It is common to have recurrent pyoderma with atopy. If there is poor response to immunotherapy and/or cyclosporine (Atopica®, Novartis), re-evaluate and treat the pyoderma. Some patients require pulse antibiotic therapy. Some patients benefit from Staphage Lysate® (Delmont Laboratories) therapy.
- Please note- 7-14 days of antibiotic therapy is almost always inadequate for pyoderma. This may seem to be effective, but remember to always treat past clinical cure.
- See appendix II for antibiotic types and choices and doses.

Malassezia

- Lipophilic; non-lipid dependent and lipid-dependent species; non-mycelial saprophytic yeast; unipolar budding fungi
- Thick, multilayered cell wall and the production of blastoconidia by repetitive monopolar (or sympodial) budding (this budding gives them the appearance of unshelled peanuts, foot prints, etc.)
- Malassezia pachydermatis is a lipophilic budding yeast that colonizes the skin and mucosal sites of healthy dogs; despite being part of the normal cutaneous microflora, it is now known that the yeast may become a pathogen under certain circumstances.
  - Malassezia pachydermatis was first identified in 1925 from scales on an Indian rhinoceros with exfoliative dermatitis.
  - Using genomic comparison and ribosomal large subunit sequencing, lipid-dependent Malassezia yeasts were further classified into six distinct taxa by Guého et al. in 1996, including M. furfur, M. sympodialis and four new species, M. globosa, M. obtusa, M. restricta and M. slooffiae, resulting in seven species under the genus Malassezia including M. pachydermatis
  - Malassezia pachydermatis is the only non-lipid dependant species, but still growth is enhanced by lipids; commensal- the yeast has been localized to the distal hair shaft, where it may occur as a commensal, but its presence in the hair follicle infundibulum is rare.
- Why do we see yeast infections with atopic dogs?
  - Zymogen (an inactive pro-enzyme, virulence factor) in the yeast cell wall is capable of activating the "complement system" → this could result in damage to keratinocyte integrity → to epidermal spongiosis, inflammation and pruritus.
  - A defective epidermal water barrier, caused either by direct keratinocyte damage or by underlying atopic dermatitis, could lead to an increase in humidity on the skin surface, thus favoring yeast proliferation. Additionally, the disrupted epidermal barrier could permit the skin immune system to be exposed to Malassezia antigens and products, eliciting inflammatory and/or hypersensitivity reactions.
  - Proteases are believed to be the mediator of itch at free nerve endings in the skin, the proteases released by Malassezia organisms could also contribute to pruritus.
  - Malassezia organisms also produce lipases (virulence factor), which alter sebum production and produce free fatty acids on the skin surface. Released lipids can be used by yeasts for nutrition. (Greasy skin coat associated with atopic dermatitis.)
- About 50% of dogs have underlying disease (e.g., atopic dermatitis)
- Breed predisposition: West Highland White Terrier, Chihuahua, Basset Hound, Cocker Spaniel, Dachshund, English Springer Spaniel, Poodle, Sheltie, German Shepherd dog, Jack Russell Terrier, Maltese, Silky terrier, Australian terrier, Collie, Golden retriever predisposed
- Clinical signs: pruritus is a major, often malodorous, greasy, thickened skin with hyperpigmentation and erythema (halo), honey color crusts
- Seasonality: often starts in summer or high-humidity months (or during "allergy season")—second spike of cases in early spring
- Diagnosis
  - Obtaining Samples: direct impression smear, acetate tape preparation, scraping, swabs, etc.; Intradermal Testing; Serology
  - Highest numbers in (clinically healthy) dogs on the chin, labial areas, perianal, interdigital spaces, claw folds, and ears.
- Management of Malassezia Dermatitis (and Otitis):
  - Goal of therapy
  - Confirm the clinical significance of the yeast in the disease process
  - Reduce the population to normal or below, enough to eliminate clinical signs
  - Maintain the population at a level unlikely to produce clinical signs
  - Treatment options: The treatment of canine Malassezia dermatitis is currently based on the use of topical and systemic antifungal therapy.
  - A combination of topical and systemic therapy may speed resolution of the disease and increase efficacy. Immunotherapy is also used.
  - Some topical agents (and examples) that can be used for Malassezia dermatitis include: Chlorhexidine (3%; Hexadine®); Clotrimazole (Otomax®, Mometomax®; Aurizon®); Enilconazole; Ketoconazole (KetoChlor®; T8-Keto®, compounded preparations), Miconazole (Malaseb®; Conifite®; Surolan®); Nystatin (Panalog®), Selenium sulphide (Selsun Blue®); Thiabendazole (Tresaderm®); Acetic Acid (vinegar)
  - It has been reported that M. pachydermatis showed sensitivity, in decreasing order of efficacy, to: Ketoconazole > econazole > clotrimazole > miconazole > nystatin
  - Some oral agents:

- Ketoconazole (Nizoral®, generic available)
  - Imidazole; inhibit prod of ergosterol (fungal cell wall) due to blocking of
  - lanosterol C14-demethylase; range 5-10 mg/kg PO q12-24 hr
  - (start: 5mg/kg PO QD)
  - give with food; monitor for GI upset (esp. cats), rarely hepatoxicity
  - antifungal and anti-inflammatory
  - secreted via the sebaceous glands onto the epidermal surface
  - anti-androgenic effects may decrease sebum production
  - consider drug interactions → potent inhibitor of cytochrome P-
  - 450 enzymes (e.g., not use with ivermectin); best to avoid in
  - cats; usually used in young to middle age healthy dogs
- Itraconazole (Sporanox® by Janssen Pharmaceuticals)
  - Triazole (see above); 5 mg/kg PO q 24 hr is a good starting dose
  - expensive at this time (no generic)
  - fewer side effects than ketoconazole; solution to be given on an empty
  - stomach; capsules to be given with food
  - good choice for small dogs and cats
- Fluconazole (Diflucan®, Pfizer; generic available)
  - Triazole (see above); 5-10 mg/kg PO q 24 hr is a good starting dose
  - lacks anti-inflammatory effect of ketoconazole
  - least hepatotoxic of azoles, primarily renally excreted unchanged
- Terbinafine (Lamasil® Novartis)
  - Allylamine; 20-30 mg/kg PO q 24 hr is a good starting dose
  - good choice for dermatophytes, effective against Malassezia
  - Name-brand is expensive at this time (generic available in USA soon, available in Canada, about $1.00/generic tablet)

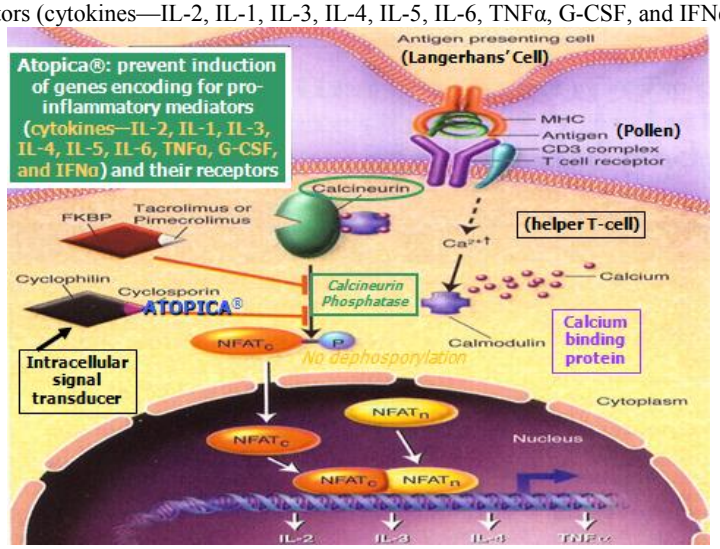
- Hints for managing malassezia
  - Look for malassezia. This is often present and commonly missed or not sought out.
  - A great degree of pruritus is often associated with the yeast infection.
  - If there is a poor response to therapy (e.g., antibiotic, immunotherapy, cyclosporine (Atopica®), consider treating for a potential yeast infection.
  - Treating for yeast infections (even if not specifically present) could prove to be beneficial for reasons other than simply controlling the yeast over population:
  - Ketoconazole may decrease leukotriene C_4 concentrations in the skin of atopic dogs, thus decreasing pruritus in the absence of yeast infection/hypersensitivity. (Marsella *et al,* 1997)
  - Azole medications increase the absorption of cyclosporine (Atopica®), thus leading to better response to therapy.
  - Treat long enough and at an appropriate and safe dose.
- Cutaneous adverse food reaction (Food allergy)
  - Diet trial is the only means of determining a food allergy. At this point in time, serology tests available are inaccurate and not worth the money (put money towards an appropriate diet trial).
  - Novel protein (e.g., kangaroo, rabbit, venison) or Hydrolyzed Diet (soy, chicken).
  - Strict for 8 weeks (if itching returns when corticosteroids are stopped, the underlying problem is unlikely a food allergy (or at least alone).
  - No treats (not even vegetables); Unflavored heartworm prevention may be indicated as perception of "flavored" suggests that "flavored" treats are okay (options: unflavored tablets, off-label oral injectable ivermectin once a month at appropriate anti-heartworm dose, topical product (e.g., Revolution®, Pfizer)
  - My personal experience is that > 10% of pruritic dogs actually are food allergic (this may be a low number as most of my cases are referred and the true food allergic dogs are not referred). I still feel it is often a good idea to rule-out a food allergy first.
  - Many clients complain about cost of allergy testing/desensitization or cyclosporine therapy (Atopica®, Novartis). I usually discuss that they are spending $50-100 already on a special diet each month!
- Dermatophytosis
  - Wood's Lamp, KOH Preparation, Fungal Culture
  - Rare in dogs. "If it looks like ringworm, it is probably bacterial."
  - History is often helpful (e.g., cats present, recent boarding, lesion distribution).
- Metabolic Disease
  - Blood Work
  - Hypothyroidism

- Cushing's Disease
- Sex Hormone Imbalance
- Testicular Tumors

- Other Conditions Associated with Pruritus: (sometimes- due to secondary infection)
  - Biopsy: rule-out several conditions (only necessary if an animal is not responding to therapy)—Examples
    - Pemphigus foliaceus vs, Pyoderma vs. Dermatophytosis vs. Demodicosis
    - Cutaneous T-cell Lymphoma vs. Secabeous Adenvitis vs. Cornification Defect
    - Cutaneous Adverse Drug Reaction vs. Hypersensitivity vs. Auto-immune
    - Alopecia X vs. Seasonal Flank Alopecia vs. Metabolic vs. Other
    - Bacterial Folliculitis (resistant) vs. Follicular Dysplasia vs. Color Dilution Alopecia vs. Other

Dermatology Rule of Thumb:
If there is a poor response to treatments, or the skin is getting worse despite treatments, always consider skin biopsies.

- Skin biopsies: Noninvasive (usually); Informative (often), Indicated in many situations. You can even get a culture at the same time. Tissue samples for culture are often better than traditional swabs. The worst case scenario is a negative biopsy, but at least this steers you in the right direction. Clinical index of suspicion is important too. A skin biopsy is a "snap-shot" in time. If the biopsy results are not what you expected, never hesitate to have them reviewed or consider performing another biopsy (multiple sites) in the near future.
- Response to corticosteroids Antihistamines & Other: Corticosteroid Trial/Response (80-90% response); Antihistamine Trial/Response (10-30% response); Pentoxifyline (Trental®); Misoprostal (Cytotec®); Essential Fatty Acids; Topical Anti-itch (e.g., Triamcinolone 0.015% (Genesis®) spray, Relief® (pramoxine), Histicalm® (diphenhydramine)
  - Other Treatments: see appendex III: other treatments
    - Omega 3 Fatty Acid Supplementation
    - Pentoxifylline
    - Misoprostal
    - Dextromorphan
    - Topical Treatments
- Allergy testing (sensitization to allergens tested): Testing, Allergen Specific Immunotherapy, & Avoidance-Cost; Response rate (~70%), Commitment (8-12 months for response, injections); Intradermal Skin Test: Testing ability of allergen to bind to mast cell (and basophil)-bound IgE or IgGd → degranulation of mast cells →release substances → inflammatory response (wheal/flare); Serological/Blood Test: Assay for increased levels of circulating allergen-specific IgE
- Atopica® (Cyclosporine capsules, USP): First oral non-steroidal treatment approved for management of atopic dermatitis (AD) in dogs; Fat-soluble, cyclic polypeptide/oligopeptide fungal product (macrolide) with immunomodulating properties - enhanced by a specific action on T lymphocytes rather than by a cytotoxic mechanism; Atopica® contains a modified formulation of cyclosporine A and forms a microemulsion in the stomach - ensures consistent absorption and well-tolerated; Lacks major adverse effects (vs. corticosteroids); Alternative to traditional therapies; Calcineurin (essential intracellular signal transducer) inhibitor-Atopica® targets intracellular signaling pathways induced by T-cell Receptor (TCR) activation when the antigen is "presented" to the T-cell (impair helper and cytotoxic T-cells)
- Atopica® = Calcineurin Inhibitor : blocks the activity of cytoplasmic calcineurin phosphatase → prevent induction of genes encoding for pro-inflammatory mediators (cytokines—IL-2, IL-1, IL-3, IL-4, IL-5, IL-6, TNFα, G-CSF, and IFNα) and their receptors



- Atopica® has strong anti-allergic effects: Block cytokine-induced activation of cells that initiate the cutaneous immune response (Langerhans' cells, keratinocytes, lymphocytes/T-cells); Decreases the number of Langerhans' cells in epidermis & inhibits the lymphocyte-activating functions of these APCs; Block cytokine-induced activation of cells that mediate the allergic reactions (inhibit mast cell and eosinophil production + protaglandin and histamine release); Inhibit growth and differentiation of B-cells (associated with IgE)
- When do I use Atopica® as labeled?: Failure to respond to immunotherapy (>80-85% respond to Atopica®), During induction phase with immunotherapy, Requiring large doses of corticosteroids, Severe conditions with chronic skin changes, Help "normalize" the skin → better natural barrier, Keratinocyte "anti-proliferative" effects, Clients who oppose (unable) immunotherapy and/or corticosteroid use, Clients desiring a more immediate solution!, Rarely used in younger dogs prior to or during immunotherapy/allergy testing, Treatment for "seasonal" allergies (e.g., 3 months a year), Healthy older dogs.
- ASIT vs. Atopica® :Poorer response to ASIT if: signs present for > 5 years, before starting ASIT- older (> 8-9 years of age), very severe chronic case; Guidelines: IDT/Serology & ASIT: 1.5 to 7 years of age; IDT/Serology & ASIT or Atopica®: 8-9 years of age; Atopica®: >10 years of age
- Successful Dosing of Atopica® : Formulation- 10, 25, 50, 100 mg capsules (blister packs); Indication- control of atopic dermatitis in dogs > 4 lbs, Initial dose-5 mg/kg (3.3–6.7 mg/kg) once daily for at least 30 days, 1 hour before or 2 hours after a meal, "jump start" with corticosteroids, baseline blood work +/- urinalysis, Maintenance dose (every other day, twice weekly, 2 days Atopica®, 1 day off, 2 days Atopica®, etc.)-based on individual response
    - Successful use of Atopica® care
        - Control infections and ectoparasites : Bacteria- Oral Antibiotics; Yeast- Oral +/- Anti-fungal medications; Fleas/mites- Flea Control
        - Appropriate dose and Adjustments -Round-up when dosing, All dogs are different
        - Review treatment details and Rechecks- Discuss possible side-effects, Discuss financial commitment , Maintain communication with clients/phone calls/e-mail
        - Educate the client (and staff)
- Corticosteroids: side effects: excessive urination (polyuria), excessive drinking (thirst) (polydypsia), overeating (polyphagia), corticosteroids: long-term effects, iatrogenic cushing's disease, calcinosis cutis, demodicosis, resistance (tachyphylaxsis), diabetes, weakened ligaments, muscle atrophy/wasting, infection susceptibility, compromised kidney function, altered electrolyte balance, vomiting, diarrhea, ulcers, etc. See appendex IV: corticosteroids
- Cyclosporine: side effects: vomiting (+/- decreased appetite), diarrhea and/or soft stools, papillomatous dermatitis (psoriasiform lichenoid dermatitis or verruciform lesions), gingival hyperplasia (possibly due to ↑ synthesis of tgfβ → fibrosis; hirsutism/hypertrichosis; epiphora (tearing)
- Cyclosporine: suspected long-term effects: (***more commonly reported in humans***): papillomavirus-associated squamous cell carcinoma in situ (vet. Derm, october 2005), systemic toxoplasmosis (cats) (vet. Derm. June 2004), bone marrow suppression, neuropathy, bacteruria +/- cystitis, involuntary shaking/tremors, reversible hepatotoxicity, renal toxicity, hypertension, increase serum cholesterol, potentially diabetogenic, +/- increases susceptibility to opportunistic infections (fungal), +/- increases susceptibility to certain malignancies (lymphoma -remains to be seen)
- Cyclosporine: long-term effects: unlikely/rare: 1 year oral toxicity study (ryffel et al., 1983)-normal beagles administered 45 mg/kg/day; side-effects: vomiting, diarrhea, anorexia, weight loss, generalized cutaneous papillomatosis, chronic hyperplastic gingivitis, periodontitis; no evidence of hepatotoxic, nephrotoxic, or myelotoxic effects; all changes reversible after 12 week recovery period; maximum non-toxic dose in dogs is 15 mg/kg/day; recommended dose is 5 mg/kg/day
    - Drug interactions & cyclosporine (csa)
        - Drugs- Increase [CSA]: Metoclopramide, Doxycycline, Erythromycin, Fluconazole, Ketoconazole, Itraconazole, Methylprednisolone, Imipenem-cilastatin, Danazol, Calcium channel blockers (e.g., diltiazem)
        - Drugs- Decrease [CSA]: Phenobarbital, Rifampin, TMS (IV), Phenytoin, Carbamazepine
        - P-glycoprotein: Transporter pump that prevents drug accumulation in cells (decrease activity), GI (e.g., CSA); BBB (e.g., IVM); other (renal, hepatic, testes, etc.); Azole drugs bind to P-glycoprotein → increase amount of CSA accumulated; Inhibitors: Ketoconazole, Itraconazole, Erythromycin, Clarithromycin, Diltiazem, Grapefruit Juice; Inducers: Phenobarbital, Rifampin, Phenytoin, St. John's Wort (note: If you have an epileptic patient receiving phenobarbital, CSA doses may need to be higher to be effective.)
        - Combination of CSA and Ketoconazole (KTZ): KTZ inhibits cytochrome P-450 in the GI & liver; KTZ inhibits P-glycoprotein in the GI - which ordinarily pumps cyclosporine into the GI; 2.5-5.0mg/kg/day PO of both KTZ and cyclosporine; give KTZ with food and the cyclosporine usually apart from food (unless vomiting); KTZ at 5mg/kg BID → 50-75% reduction in CSA; dose (5mg/kg once daily seems helpful enough)
- Treatment Indications for Cyclosporine: Atopic Dermatitis (Atopica®)-approved use: Sebaceous Adenitis; Primary Seborrhea (Cockers); Perianal Fistula; Erythema Multiforme; Actinic Dermatitis; Immune-mediated Disease: PF/PE/DLE; Eosninophilic Dermatitis : (e.g., cats); Pruritic Diseases; Dirty Face Syndrome (Persian & Himalayan); Ulcerative Dermatosis of the Philtrum of St. Bernards and Newfoundland dogs; Sterile Pyogranulomatous Syndrome; Sterile Nodular Panniculitis; Interdigital Furunculosis;

German Shepherd dog deep Pyoderma/Metatarsal Fistulae; Follicular Hyperkeratosis of Cocker Spaniels; Feline Acquired Alopecia; Feline Urticaria Pigmentosa; Cutaneous Histiocytosis; Other: MM-MG, thyroiditis, neuritis, uveitis, arthritis, etc.

Appendix I: Flea therapy choices. See topical therapy part II

Antibiotics (Review)

Inhibit protein synthesis

50 s (ribosomal subunit)	**30 s (ribosomal subunit)**
• Lincosamides (lincomycin & clindamycin) • Azalides (azithromycin & clarithromycin) • Macrolides (erythromycin, tylosin) • Chloramphenicol (used more)	• Tetracycline- (if C&S) • Aminoglycosides (side-effects, better Gram negative, topical/injection

NOTE: All are bacteristatic except aminoglycosides (bactericidal).

Inhibit cell wall synthesis

- Cephalosporins (commonly used)
- Vancomycin (injection only)
- Bacitracin (topical)
- Penicillins (w/o clavulanate = bad for skin disease)
    - Note: All are bactericidal.
- Affect Metabolism: sulfonamides/trimethoprim (effective for skin); rifampin (combination)
    - Note: Both are bactericidal.
- Inhibit DNA gyrase & topoisomerase: fluoroquinolones (bactericidal)
    - Other: mupirocin and fusidic acid (topical, bacteristatic), polymyxin (topical, bactericidal)

Susceptibility to Anaerobes

- >90% - metronidazole, Clavamox®
- 75-90% - lincomycin and cephalosporines
- 50-75% - erythromycin

Appendix II: Antibiotic types, choices, and doses.

Brief Overview of Antibiotics used in Veterinary Dermatology

Drug Class	Selected Medications and Canine Doses	Mode of Action and Elimination	Indications	Advantages, Disadvantages & Other Information
Lincosamides	Lincomycin (Lincocin®, Pfizer): 22-25mg/kg PO BID Clindamycin (Antirobe®, Pfizer, generic): 11 mg/kg PO QD or BID	MOA: Inhibits bacterial ribosomal protein synthesis (50 S); inhibits protein chain elongation (initiation); bacteriostatic Elimination: Liver > kidney	Gram-positive cocci, Gram-positive anaerobes (*Clostridium*) and Gram-negative anaerobes, *Actinomyces, Leptospira, Mycoplasma*.	Good agent for superficial pyoderma, usually BID PO, reasonable to moderately expensive, NOT for gram negative aerobes Cross resistance with erythromycin, absorption reduced if administered with food (lincomycin, risk of nausea)
Azalides (macrolide)	Azithromycin (Zithromax®, Pfizer): 5-10mg/Kg PO QD 7-14 days Clarithromycin (Biaxin®, Abbott): 2.5-10mg/kg PO BID	MOA: Inhibits bacterial ribosomal protein synthesis (50 S); bacteriostatic Elimination: Liver > kidney	some Gram-positive cocci, Gram-positive anaerobes (Clostridium) and Gram-negative anaerobes, *Actinomyces*, *Leptospira*, *Mycoplasma, Toxoplasmosis,* Gram-negative (*Pasturella)*	expensive, less action for Gram-positive cocci, better for *Toxoplasmosis*, still a reasonable agent for superficial pyoderma Cross resistance with erythromycin, absorption reduced if given with food
Macrolides	Erythromycin (generic): 10mg/kg PO TID	MOA: Inhibits bacterial ribosomal protein synthesis (50 S), translocation; bacteriostatic Elimination: Liver > kidney	Gram-positive cocci, *Mycoplasma, Leptospira*	Vomiting and diarrhea bacteriostatic agent for superficial pyoderma, GI (V+ in about 20% of cases), reltively inexpensive, resistant for Gram-negative still a reasonable agent for superficial pyoderma (not used as much anymore)
Tetracycline	Tetracycline ≥15kg = 250mg PO TID <15kg = 500mg PO TID Minocycline Doxycycline (generic): 5 mg/kg PO BID	MOA: Inhibits polypeptide (protein) synthesis, bacteriostatic inhibit attachment to tRNA (binds aminoacyl tRNA); energy dependent Metabolism: Kidney: 60% urine unchanged (tetracycline); 10% (mino); Liver: 40% (tetracycline); 90% (mino); GI: feces (i.e., doxy)	Gram-positive cocci; used with niacinamide for immuno-modulatory properties	Bacterial resistance develops easily, may cause gastric irritation and vomiting (GI upset) used for superficial pyoderma (ONLY if susceptible on C&S) Minocycline and Doxycycline better choice; reportes of vomiting and diarrhea as well as *chelating (bones/teeth)*
Amino-glycosides	Gentamicin, Kanamycin, Tobramycin, Amikacin	MOA: Binds with bacterial ribosomes, bactericidal Metabolism: Kidney: (glomerular filtration)- without tubular reabsoption	Gram-positive cocci, Gram-negative rods	Renal toxicity, administered by injection or topical (ears), resistant populations are increasing, ototoxicity (controversial), great for life threatening disease or mixed bacterial infections, rarely necessary in the treatment of pyoderma,expensive, requires close monitoring

Chloramphenicol	Chloramphenicol (generic): 40-50 mg/kg PO TID	MOA: Inhibits ribosomal protein synthesis bacteriostatic - inhibit attachment to tRNA (binds aminoacyl tRNA) Metabolized and Excreted: Mostly liver- via glucuronide conjugation; excretion	Gram-positive and Gram-negative spectrum, non-ionizable hence diffuses readily into extravascular fluids (crosses blood-brain barrier)	*In vitro* testing does not always correlate with *in vivo* activity, especially in deep pyoderma, potentially toxic to bone marrow, increasing concern about human exposure - idiosyncratic aplastic anemia (inhibit uptake of Fe by RBC), pancytopenia, immunosuppression, blood dyscrasia, GI, anorexia, D+, glossitis, skin rash, myocardiac depression Very good in superficial pyoderma, poor in deep or mixed pyoderma, inexpensive; used more with increased resistance
Cephalosporins	Cephalexin (Keflex® Advancis, generic): 25-30mg/kg PO BID (also 22-25mg/kg PO BID-TID) Cefadroxil (Cefa-Tabs® and Cefa-Drops®, Fort Dodge): 22-25mg/kg PO BID Cefpodoxime proxetil (Simplicef®, Pfizer): 5-10 mg/kg PO QD Cefovecin (Convenia®, Pfizer): injection q7-14 days (Spring, 2008 in USA)	MOA: Inhibit cell wall synthesis by interfering with polypeptide cross linkages, bactericidal; Prevent cross-linking of peptidoglycan chains by block PBP or transpeptidase Metabolism: Kidney: 1^{o} urine- (glomerular excretion > tubular excretion)	Gram-positive cocci and many Gram-negative bacilli	Overuse and abuse is leading to resistant strains, some cross sensitization with penicillins; (15% humans), possible glucosuria Inexpensive (relatively), excellent broad spectrum antibiotic when used appropriately, BID or TID Good choice for pyoderma (some consider as a good 1st choice, others save this as a 2nd line of defense) Other: (cefoperazone & cefpiramide)- metabolized by bile; some effective against *Pseudomonas* (e.g., ceftazidime, ceftazidime, cefperazone, cefotaxime, ceftizoxime, cefepime)
Penicillin (synthetic)	Amoxicillin, Ampicillin, Carbenicillin Oxacillin* (Bactocill®): 22 mg/kg PO TID	MOA: Inhibits cell wall synthesis, bactericidal Prevent cross-linking of peptidoglycan chains by block PBP or transpeptidase Metabolism: Kidney: 1^{o} urine- (tubular excretion > glomerular excretion)	Gram-positive cocci (Staphlococci) that do not elaborate penicillinase, some gram-negative bacteria Exception: Oxacillin; Penicillinase resistant *Staphylococcus intermedius*	Inactivated by penicillinase produced by some Staphylococci and many gram-negative organisms, degraded by gastric acid, limited gram-positive spectrum Bad choice for pyoderma Exception: Oxacillin: Expensive, poorly absorbed in dogs, administer one hour prior to feeding, TID dosing; Excellent agents for *Staphylococcus intermedius* pyoderma, expensive—thus Oxacillin not used much anymore

Penicillin (potentiated)	Amoxicillin + Clavulanic Acid (Clavamox®, Pfizer): 15-20 mg/kg PO BID to TID	See above; Clavulanic acid will compete with Staphylococcal penicillinase and thus "shields" the antibiotic	Penicillinase resistant *Staphylococcus intermedius*	Expensive, TID > BID dosing; higher than label dose for pyoderma; - less effective than theoretical considerations would indicate, efficacy may not warrant expense unless no other choice (for large dogs); reasonable choice for pyoderma
Fluroquinolone	Enrofloxacin (Baytril®, Bayer): 5-20 mg/kg PO QD Ciprofloxacin (Cipro®, Bayer, generic): 15-20mg/kg PO QD Orbifloxacin (Orbax®, Schering Plough): 2.5-7.5 mg/kg PO QD Marbofloxacin (Zenaquin®), Pfizer): 2.75-5.5 mg/kg PO QD Difloxacin (Dicural®, Wyeth): 5-10mg/kg PO QD	MOA: Inhibits bacterial *DNA gyrase (topoisomerase II);* bactericidal Metabolized: liver; 2^{o} excretion Excretion: 1^{o} urine (renal tubular and glomerular filtration)	Gram-negative bacilli, and Gram-positive cocci	*Pseudomonas aeruginosa* commonly will be resistant, only 25% efficacy against anaerobes (except pradofloxacin- much broader spectrum), possible glucosuria Good broad spectrum antibiotic, excellent tissue penetration (even with mucopurulent (wbc) material present, unlike other, i.e., AG), save for deep infections, scarred lesions and mixed infection, primary use is for Gram-negative bacilli, expensive, Other Choices: Ibiflocacin (Ibaflin® gel)- Europe Pradifloxacin (Veraflox®, Bayer)- Unavailable
Sulfonamides (potentiated-diaminopyrimidine)	Sulfadiazine + Trimethoprim (Tribrissen®, Schering Plough generic): 15 mg/kg PO BID Sulfa-methoxazole + trimethoprim (generic): 15 mg/kg PO BID Sulfa-dimethoxine + ormetoprim (Primor®, Pfizer): 27.5 mg/kg PO QD	Inhibits bacterial protein anabolic enzymes; Interferes bacterial synthesis of PABA from folic acid, bactericidal Compete with PABA + DHFR (potentiated) Metabolized in liver, excreted in urine Hydroxy-alamine reductase: enzyme in liver microsomes and in peripheral blood cells allow the removal of toxic hydroxylamine	Gram-positive cocci and some Gram-negative bacilli	*In vitro* testing does not always correlate with *In vivo* activity, should not be dosed above recommended dosage regimens due to precipitation in the urinary tract (crystals), induction of KCS, the most frequent cause of drug eruptions in the dog, visceral drug reactions including hepatic necrosis, enhanced genetic susceptibility of the Doberman Pinscher (decreased ability to metabolize hydroxalamine) for the development of drug-induced eye and joint disease, altered thyroid activity; poor efficacy in pus Good broad spectrum antibiotic (but SEs), inexpensive, advantage of twice daily administration, worry about potential for drug eruptions, EM, PF, etc. (monitor blood work and STT); **Primor®- less side effects, no KCS, more expensive, convenient

Rifampin	Rifampin (generic): 5-10mg/kg PO QD-BID *start at 5 mg/kg PO QD)	Nucleic acid RNA synth inhibitor; inhibit DNA dep RNA polymerase	Bacterial infections based on culture and sensitivity	used more with increased resistance- must use with an additional antibiotic (e.g., clindamycin) because prone to developing resistance symptomatic hepatitis, increase hepatic enzymes in dogs, thrombocytopenia, hemolytic anemia, anorexia, V+/D+, orange color sweat, urine, tears, feces, saliva
Linezolid	Linezolid (Zyvox®): 10mg/kg PO BID	MOA: stopping the 30S and 50S subunits of ribosome from binding together; binds on the 23S portion of the 50S subunit close to the peptidyl transferase and chloramphenicol binding sites→ stops the interaction with the 30S subunit.	Multi-resistant bacteria including streptococcus and methicillin-resistant *Staphylococcus aureus*/intermedius (MRSA/MRSA).	Oxazolidinone class; very expensive, controversial- should we use in veterinary medicine; SE: nausea, poor appetite, diarrhea, nausea, fever, constipation,thrombocytopenia, Weak monoamine oxidase inhibitor (MAOI) and should not be used with certain medications.

Prepared by IBS (2007; Updated Oct., 2009) - Please always check doses prior to administering medications to patients.

Selection of topical antibiotics

- Mupirocin 2% (block isoleucine tRNA synthetase→ stop protein synthesis)- mostly Gram-positive, excellent penetration
- Retapamulin (Altabax®): first pleuromutilin; inhibition of bacterial protein synthesis by binding to the prokaryotic ribosome; mostly Gram-positive (e.g. MRSA), excellent penetration 10 mg retapamulin/1g of ointment in 5, 10, and 15 gram tubes; expensive (average = $40-85/tube)
- Bacitracin (inhibit cell wall synthesis by interfering with carrier)- gets primarily Gram positive
- Polymyxin B (cationic detergent that damages cell membrane function)- gets Gram negative; excellent for Pseudomonas
- Neomycin (AG = protein synthesis inhibitor); Gram negative and positive
- Silver sulfadiazine (heavy metal poisoning- silver transported across cell wall; competitive inhibitor of PABA); excellent for Pseudomonas
- Fusidic Acid (inhibit protein synthesis by altering translocation of polypeptide units and elongation)

Appendex III: Other treatments

Antihistamine trial/response (30% response) (Selected examples)

- Ethanolamine (Aminoakyl Ester) Derivative
  - Clemastine (Tavist-1®); Diphenhydramine (Benadryl ®)
- Ethylenediamine Derivatives
  - (rarely used)
- Piperazine Derivative
  - Hydroxyzine (Atarax®); Meclizine (Antivert®) & Dramamine II ®)
  - Cetrizine (Zyrtec®)
- Piperidine Derivatives
  - Loratadine (Claritin®); Fexofenadine (Allegra®)
  - +/-Cyproheptadine (Periactin®)
- Propylamine (Alkylamine) Derivatives
  - Chlorpheniramine (Chlor-Trimeton ®)
- Phenothiazine
  - Trimeprazine (Temaril®)- combined with prednisolone (Temaril-P®)

Non-antihistamine choices with anti-histamine properties (Selected examples)

- Tricyclic anti-depresent (TCA)
  - Doxepin (Sinequan®, Adapin®)
  - Amitryptyline (Elavil®)

Canine/Feline antihistamine therapy

Name	Forms Available	Dosage/Interval	Other
Hydroxyzine Pamoate or HCl (Atarax®, Vistaril®)	Capsules: 10mg, 25mg, 50mg, 100mg Syrup: 10mg/5ml	Dog: 2.2mg/kg BID-TID Cat: 10mg/cat BID	Hyperexcitability in cats
Amitriptyline (Elavil®)	Tablets: 10mg, 25mg, 50mg, 100mg	Dog: 1.1-2.2 mg/kg BID Cat: 5-10 mg/cat QD-TID	Not use if cardiovascular disease, seizure, MAO (i.e., Mitaban, Preventick collar); SE: salivation, disorientation, ataxia, GI
Chlorpheniramine Maleate (Chlor-Trimeton®)	Tablets: 2mg, 4mg (readily available OTC), 8mg, 12mg Syrup: 2mg/5ml	Dog: 0.2-0.8 mg/kg BID-TID Cat: 2-4 mg/cat BID	
Clemastine Fumarate (Tavist®)	Tablets: 1.34mg, 2.68mg	Dog: 0.05-0.1 mg/kg BID Cat: 0.68 mg/cat	
Diphenhydramine HCl (Benadryl®)	Capsules or Tablets: 12.5mg, 25mg, 50mg Syrup: 2.5mg/ml	Dog: 2.2 mg/kg BID-TID Cat: 2.2mg/kg QD-BID	Hyperexcitability in cats
Doxepin HCl (Sinequan®, Adapin®)	Capsules: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	Dog: 0.5-1.0 mg/kg to 3.0-5.0 mg/kg BID	Not use if glaucoma patients.
Cyproheptadine HCl (Periactin®)	Tablets: 4mg	Dog: 0.5-1.1 mg/kg BID-TID Cat: 2 mg/cat BID	Poor choice for pruritus.
Cetirizine HCl (Zyrtec®- now OTC)	Tablets: 5mg & 10mg Syrup: 1mg/ml	Cat: 2.5-5mg PO QD-BID Dog: (0.5-1.0mg/kg PO QD-BID) <10 lb = 2.5 to 5mg PO QD 10-15 lb = 5mg PO QD 15-39 lb =10 mg PO QD >40 lb =10 mg PO BID	Blocking allergen-induced late phase cutaneous reaction and decrease influx of eosinophils in response to allergens
Loratidine (Claratin®; Alavert®; generic)	Tablets: 10mg tablets and Reditabs™; Syrup: 1mg/ml syrup	Dog: <10 kg = 2.5 mg PO QD 10-15 kg = 5 mg PO QD 16-39 kg = 10 mg PO QD or 5mg PO BID 40-69kg = 10 mg PO BID >70 kgs = up to 15 mg PO BID	0.25 mg/kg-0.50 mg/kg orally every 24 hours
Fexofenadine (Allegra®)	Tablets: 30mg, 60, 180mg Syrup: 30mg/5ml	Cat: < 10lbs =10mg PO BID Dog: < 10lbs = 10mg PO BID 10-20lb = 30 mg PO QD 20-34lb = 60 mg PO QD 35-49lb = 120mg PO QD	

Pentoxifylline (Trental®)

- Methylxanthine drug type.
- occasional effectiveness for controlling atopy; moderately effective adjunctive treatment for canine AD; well tolerated in dogs; used more for ischemic disease (e.g., peripheral arterial disease (PAD) in humans- increases the amount of oxygen that reaches tissues via increasing the flexibility of red blood cells)
- Phosphodiesterase inhibitor with multiple immunomodulating properties; suppresses TNF-alpha, IL-1, and IL-6; reduces infiltration of inflammatory cells into tissues
- Efficacy seems to be dose dependent: half life is short thus 3x/day is better than 2x/day; dogs with grass allergy respond better than dogs allergic to HDM and molds; older dogs respond better than younger dogs; skin lesions and pruritus improved on 10 mg/kg bid but did not resolve
- Side Effects: nausea, vomiting, diarrhea (rarely reported)
- Note: Ciprofloxacin may increase serum levels.
- Dose: 15-20 mg/kg PO TID (doses vary) or 25mg/kg PO BID

Misoprostal (Cytotec®)

- Prostaglandin E1 analogue with anti-allergic effects.
- Minimal effectiveness for controlling atopy (30% will decrease in level of pruritus and skin lesions)
- Side Effects: nausea, vomiting, loss of balance, diarrhea (rarely reported); Gastrointestinal side effects vomiting and diarrhea in 6 of 18 dogs limit usefulness.
- PGE1 increases cAMP - stabilizes cells and blocks secretion of pro-inflammatory cytokines; strong anti-allergic properties in people
- Dose: 5mcg/kg of misoprostol TID

Dextromethorphan hydrobromide (Robatussin®)

- Cough suppressant and anti-pruritic effects (Dodman NH, Shuster L, Nesbitt G, et al. The use of dextromethorphan to treat repetitive self-directed scratching, biting, or chewing in dogs with allergic dermatitis. J Vet Pharmacol Ther 2004;27:99-104). N= 14 dogs with atopic dermatitis; dogs received 2 mg/kg BID dextromethorphan (gelatin capsule); during the study, oatmeal soaks were allowed, but no other therapies; 10 completed the study, dogs receiving placebo had itch behaviors 8.7% of the time and dogs receiving dextromethorphan exhibited itch behaviors 6% of the time (difference 2.7%- statistically significant); 31% decrease in observed itch behaviors; dextromethorphan was beneficial in reducing the time the dogs spent licking, chewing, and self-biting.
- Understand that the 31% decrease in itching represents 23 minutes of itch-scratch behavior for placebo and 17 minutes for the dextromethorphan; thus a decrease of 6 minutes of itching overall; not truly that impressive and the drug has a short half-life, is cleared rapidly, and has poor bioavailability (2. Kukanich B, Papich MG. Plasma profile and pharmacokinetics of dextromethorphan after intravenous and oral administration in healthy dogs. J Vet Pharmacol Ther 2004;27:337-341).
- May not be a great option, never-the-less still worth trying if necessary.
- Do not use within 14 days of using monoamine oxidase inhibitors (MAOIs); Do not use with other sedatives, narcotics, antihistamines, or central nervous system depressants as effects of the drugs would be increased; No known food interactions;
- Side Effects: sedation, diarrhea, vomiting, excitement, loss of balance, disorientation, lethargy, decreased rate of breathing.

Essential Fatty Acid Therapy (Essential fatty acids cannot be synthesized so supply in diet.)

(2) Broad groups

Omega 3 Fatty Acids	Omega 6 Fatty Acids
green leafy vegetables, seaweed, fish, flaxseed oil, linseed oil	vegetables, primrose, borage, black current, other
alpha-linolenic acid (ALA)- flaxseed/linseed eiscocapentaenoic acid(EPA)- fish & seaweed docosahexaenoic acid (DHA)- fish & seaweed	linoleic acid (LA) – vegetable, seeds, sunflower, safflower, soy, canola arachadonic acid (AA)- EFA for cats (no *delta-6-desaturase*)
EPA competes with arachadonic acid as substrate COX, 5-LOX, and 15-LOX, form mediators that inhibit LTB4 (pro-inflammatory LT)	LA converts to GLA→ DGLA→ competes with arachadonic acid as substrate COX, 5-LOX, and 15-LOX

Note: gamma-linolenic acid (GLA) – promrose, borage, black current, flaxseed and dihomo-gamma-linolenic acid (DGLA) are Omega-6 fatty acids, but not essential

- Inflammation associated with allergic skin disease may be in part due to abnormal EFA metabolism and inappropriate eicosanoid synthesis (skin lacks enzymes necessary to convert EPA (Omega 3) or LA (omega 6) to AA (delta 6 and 5 desaturase); skin is able to "elongate" EPA→ DHA (Omega3) and GLA→ DGLA (Omega 6); thus supplementing with GLA may mean more GLA in skin and more DGLA (DGLA not converted to AA because skin lacks the enzymes)
- Cell membrane phospholipids, prevent water lose from skin
- Why try fatty acid supplementation and why may it work?

- EPA & DHA (Omega 3) and DGLA (Omega 6) in skin cell membranes can decrease skin inflammation via competition with AA for metabolic enzymes.
- Modulate leukotriene and prostaglandin synthesis.
- Eicosanoids are anti-inflammatory.
- Restore normal composition of lipids to skin (barrier function) & modulate lymphocyte functions.
- Ratio of Omega 6:Omega 3 (1-5:1) vs. Omega 3 alone (controversial and unknown)

- Goal: decrease in the inflammatory (AA derived) eicosanoids (inflammatory mediators) and this an increase in more of the "less" inflammatory mediators
- Dose: varies

Dose for inflammatory disease associated with skin disease

Fatty acid	Dose
Omega 3	50-250mg/kg/day
Omega 6	See ratio

- Small Dog (Goal): 250-300mg EPA/day or 500-600mg EPA EOD and 175mg-200mg DHA/day or 350-400mg DHA EOD
- Middle Dog (Goal): 500-600mg EPA and 350-400mg DHA
- Large Dog (Goal): 1000-1200mg EPA and 700-800mg DHA

- Side effects are rare, pancreatitis and diarrhea.
- May have corticosteroid sparing effect and/or synergistic effect with antihistamines.
- Diets high in Omega 3 Fatty Acids: Examples:
  - Purina® JM (Joint) Diet
  - Hills® N/D (Cancer) Diet > J/D (Joint) Diet >D/D (Skin/Allergy) Diets

Supplements (examples): Note: diets & high levels (e.g., prescription Hill's d/d diets)

- 3V Caps® (IVAX)
  - Large & Giant Breeds 417mg Omega 3/capsule
  - Medium & Large Breeds 300mg Omega 3/capsule
  - Small & Medium Breeds 171mg Omega 3/capsule
- DermCaps®ES (IVAX)
  - One Size 123mg Omega 3 - 368mg Omega 6/cap.
- DermCaps®Regular (IVAX)
  - One Size 108mg Omega 3 - 402mg Omega 6/cap.
- Allerderm EFA Caps HP (Virbac)
  - One Size 200 mg Omega 3 - 87 mg Omega 6/cap.
- EicosaDerm® (Dermapet)
  - Liquid 600mg Omega 3/Pump

Leukotriene inhibitors (zileuton (zyflo®, critical therapeutics)

- poor control of pruritus; helpful with erythema
- 5 lipo-oxygenase inhibitor useful and safe in humans (used for atopy)
- Side Effects: insignificant
- Dose: 5 mg/kg PO TID

C-kit tyrosine kinase inhibitor

- e.g., Imatinib mesylate (Gleevec®; Novartis)-- to treat chronic myeloid leukemia (in people); Masitinib (Kinavet®; AB Science- 50% response reported)-veterinary product
- potential treatment for systemic mastocytosis, mast cell tumors (humans and dogs); shows promise as an oral therapy for atopy (humans and dogs); clinical trials/investigations are currently taking place for use in veterinary medicine

Janus kinase inhibitors (JAK)

- JAK Pathway- intracellular pathway that drives itch/inflammation in skin
- Cytokine (e.g., IL-31 and IL-4) bind to receptors on cell membranes → activates JAK pathway(s) → activate intracellular proteins (STAT = signal transducer and activator of transcription) → gene transcription → biologic response (e.g., itching)
- Oclacitinib: novel JAK inhibitor (JAK 1 and 3 inhibitor)- AK 1 & 3 enzymes play essential role in cytokine signaling in AD (inhibits IL-31)
- Pfizer developing this medication.

Gabapentin or pregabalin

- Blocks voltage-gated calcium channels

- Gabapentin- 10mg/kg PO BID to TID

Maropitant (cerenia®)

- NK-1 antagonist, blocks Substance P
- Possible efficacy against itching.

Topical treatments

Corticosteroids

- e.g., Triamcinolone 0.015% (Genesis®) spray

Analgesics

- e.g., Relief® (pramoxine)
- Antihistamine:
- Histicalm® (diphenhydramine)
- Calcineurin Inhibitirs: (decrease erythema > decrease pruritus)
- Elidel®- Novartis (pimecrolimus); Protopic®-Fujisawa (tacrolimus)

Capsaicin

- Capsaicin is a derivative of chili pepper; decreases pain and itch.
    - Mechanism of action unknown- depletion of substance P (SP) from sensory nerve endings humans, there is evidence that SP plays a role in AD; SP release is triggered by allergen challenge and by histamine; SP receptors have been identified on mast cells; SP is chemotactic for neutrophils, monocytes, T cells, and eosinophils; induces the expression of cell adhesion molecules; induces proliferation of T helper lymphocytes
    - No difference in SP concentration between normal and AD dogs, but this may be helpful as a topical therapy (Marsella et al, 2002)
    - May be helpful for acral lick dermatitis/granulomas.

Appendex IV: Corticosteroids

Mechanism of action

- Increase production of lipocortin-1 → reduce action of phospholipase A2 on cell membranes--> inhibit AA cycle this decrease inflammation
    - block action of phospholipase A2 on cell membranes--> inhibit metabolism of AA cascade (thus no PG or LT)
- Decrease inflammation by decreasing the formation of PG and other inflammatory mediators
- Avoid further inflammation & tissue damage by preventing lytic enzymes from being released
- Act mainly by repression of inflammatory genes such as cytokines, adhesion molecules, inflammatory enzymes and receptors.
    - Decreased production of collagenase, elastase, plasminogen activator,
    - Inhibit synthesis or release of TNF, IL-1, IL-2 IL-6, IL-8; also: INF
- Act partly by inducing anti-inflammatory genes such as secretary leukocyte proteinase inhibitor, lipocortin-1 (lipomodulin), interleukin-1 receptor antagonist.
- Increased production of cytokine receptors and neutral endopeptidase.
- Decrease attraction of more inflammatory cells
- Prevent swelling & loss of fluids from systemic circulation (decrease capillary permeability)→ decrease vascular permeability
- Decrease eosinophil and mast cell survival and production
- Suppress Ab production at high doses (may suppress IgE levels)

Detailed mechanism: Inhibitory effects on transcription factors AP-1 & NF-κB

- NF-κB is regulator of genes for many cytokines and cellular adhesion molecules.
- NF-κB is usually bound to a second protein IκBα in the cytoplasm of unstimulated cells which prevents it entering nucleus.
- Signaling of the cell phosphorylates IκBα and releases NF-κB which translocates to nucleus and affects gene transcription.
    - GCs increase transcription, synthesis and cytoplasmic concentration of IκBα
    - GCs decrease synthesis of a number of proinflammatory molecules such as cytokines, interleukins and proteases (A benefit of GC in therapy.)

Advantages	Disadvantages
inexpensive, very effective, quick response (put the "fire" out)	PU/PD, tachypnea, PP, change behavior, GI signs, pancreatitis (change viscosity of enzymes & thinning of strux/leak) CC, infx (staph/yeast), demodicosis, thin dermis, comedones, poor wound healing, weak ligaments (ACL), osteoporosis, steroid hepatopathy, incr lipid, DM, change CBC/CHEM (q6 months; ACTH-stimulation); dermatophyte (i.e. *T. rubrum* growth enhanced w/ hydrocortisone present!

Note: adrenal suppression (give PO EOD to address this problem)- wean slowly

When to use corticosteroids?

- Avoid/minimize use of injectable formulations for pruritus/atopy in dogs (only short acting formulations for acute vaccine/drug reactions); oral corticosteroids take effect in about 30-60 minutes and if a dog has been pruritic for weeks, 30 minutes will not make a difference and oral administration allows for easier control/titration.
- To control the pruritus in the "acute" phase.
- Short-term management (e.g., seasonal allergy < 2 months).
- During immunotherapy induction (low and infrequent dosing).
- Address flare-ups.
- Drug reactions and auto-immune skin disease.
- Mange flea allergy dermatitis or pruritus associated with sarcoptic mange.
- Jump-start a patient with this medication sometimes when starting Atopica®.
- Mange severe ear disease.
- Manage older patients (arthritic or multiple underlying disease) requiring a minimal amount of prednisone/prednisolone (e.g., 65 pound dog getting 1-2 Temaril-P three days a week). This assumes that the skin is not lichenified and hyperpigmented (Atopica® helps "normalize" the skin barrier.)
- Help rule-out food allergies/rule-in environmental allergies.

Corticosteroids

Side effects

Excessive urination (Polyuria); Excessive drinking (thirst) (Polydypsia); Overeating (Polyphagia); Pot Belly (laltered lipid metabolism; redistribution of fat); Blood work changes (cbc/chemistry)

Long-term (Possible) effects

Demodicosis, Iatrogenic Cushing's Disease, Resistance (tachyphylaxsis), Diabetes (gluconeogenesis (muscle wasting)→ glycogen laid down in liver & increased insulin resistance → +/- hyperglycemia), Weakened Ligaments, Muscle Atrophy/Wasting, Infection Susceptibility (UTI, pyoderma), Calcinosis Cutis, Compromised Kidney Function, Altered Electrolyte Balance, Vomiting, Diarrhea, Ulcers, Osteoporosis- increased elimination of calcium & phosphate

Corticosteroids Possible Effects on Skin: Calcinosis cutis, Telogen phase extended (fail to re-grow hair/alopecia) (not in horses), Skin atrophy & wrinkles (stria) - lose of collagen & elastin, Vessels prominent & easily bruise (loss of structural support for cutaneous vessels), Flaky/dry/scaling skin (due to decreased sebum production)

Three factors that influence effect

1. Potency (increased by adding synthetic compounds -methyl & fluoride)
2. Duration of Action (increased by adding synthetic compounds (methyl & fluoride)
    a. Administration
        1) PO is rapidly absorbed (free base or esters)
        2) IV/IM are given as esters
            a) Acetate- insoluble
            b) Diacetate- insoluble
            c) Phosphate- soluble
            d) Succinate – soluble
    b. Water Solubility
        1) Slowly absorbed:
            a) slow release/prolonged absorption
                i. Acetate- water insoluble
                ii. Diacetate- water insoluble
        2) Rapidly absorbed:
            a) quick release/rapid absorption
                i. Phosphate- water soluble
                ii. Succinate - water soluble
3. Protein Binding
    a. Only free glucocorticoid is metabolically active, & many synthetics are poorly protein bound → high potency at low doses
    b. "Corticosteroid binding globulin" is a specific glycoprotein that binds glucocorticoids (with low binding capacity) & with large doses, the capacity is exceeded & albumin becomes the protein for binding
    c. Animals with low albumin have a decreased binding capacity, thus more is unbound (e.g., metabolically active), thus may have more toxicity

Common injection treatments available (examples)

- Weeks: Acetate & Diacetate (avoid in dogs)
    - Methylprednisolone acetate (Deo-Medrol®, Pfizer)
    - Triamcinolone acetonide (Vetalog®, Fort Dodge)

- Hours/days: Phosphate & Succinate (safer, but PO usually adequate)
    - Methylprednisolone sodium succinate (Solu-Medrol®, Pfizer)
    - Dexamethazone sodium phosphate (Azium®, Schering Plough)
    - Prednisolone sodium succinate (Solu-Delta-Cortef ®, Pfizer)

Common oral treatments available (examples): (please check doses if unsure.)

Predniso(lo)ne: (initial doses, then taper)

- Stress/inflammation/trauma
    - 0.1-0.2mg/kg/day
- Anti-inflammatory
    - 0.5-1.0mg/kg/day (dog)
- Autoimmune/immunosuppressive
    - 1.0-2.2mg/kg/day (dog)
    - 2.2-4.4mg/kg/day (cat)

Methylprednisolone (medrol®)

- 4/5 (80%) the dose of prednisolone
- rule: 5mg prednisone = 4mg methylprednisolone
- less immediate SE's

Triamcinolone (vetalog®)

- 1/7 to 1/10 dose of prednisone
- Anti-inflammatory
    - 0.03-0.075 mg/kg QD (tapered to 48-72 hrs); can increase slightly for the first few days to "knock-down" the itching (0.1-0.2 mg/kg/day)
- Autoimmune (QD then taper to q 2-3 days)
    - 1.5 to 2.2 mg/kg/day (dog)- or start a little lower
    - up to 4.4mg/kg/day (cat)- start at 2-3mg/kg/day and taper (risk induced diabetic)

Dexamethasone (azium®)

- 1/7 to 1/10 dose of prednisone (0.1-0.2 mg/kg QD few days and taper to 0.025mg/kg 3-5 days and then q 2-3 days
- Autoimmune: 0.1-0.6 mg/kg (dog/cat) - QD until remission, then taper to q 3 days

Common topical treatments available (examples for anti-inflammatory purpose)

(Potency: flucinolone> betamethasone > dexamethasone > triamcinolone > hydrocortisone)

- Potent
    - Betamethasone (Otomax®; Mometomax®; Gentocin® Spray)
    - Dexamethasone (0.1%) (Tresaderm®; Aurizon®; Tobradex®)
    - Flucinolone (0.01%); SynOtic® (flucinolone + DMSO)
- Moderate
    - Triamcinolone (0.1%); Panalog®; Animax®; Genesis® Spray)
    - Isoflupredone acetate (0.1%); Tritop®; NeoPredf®
- Mild
    - Hydrocortisone acetate (0.2 & 1.0%) (Bur-Otic®)
    - Prednisolone (0.17%); LiquiChlor®/compound available; Surolan®

References are available upon request