ATOPIC DERMATITIS: CURRENT CONCEPTS AND THERAPY

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INTRODUCTION

Each year Veterinary Pet Insurance publishes a list of top 10 claims for veterinary patients. For dogs, the number one claim is Allergic Dermatitis second is Otitis Externa, and third is Bacterial Skin Infection. To a dermatologist, these 3 things are all clinical manifestation of the same underlying process: Atopic Dermatitis. This is an exciting time to be a veterinarian because our understanding of the most common disease we see and manage is changing. New information is emerging that has dramatically changed our understanding of the physiology of itch and the genetic and environmental factors that result in the disease we recognize as Atopic Dermatitis. Curiously our new understanding of this important disease is very different from what we learned in school as short as 5-10-15 years ago.

What I Learned in School

The traditional understanding I was taught in school was that Atopy was similar to hayfever in people. It was triggered by abnormal immune response to inhalant allergens such as pollens, molds, house dust, house dust mites, etc; except that dogs itched and people sneezed. The whole process was dependent on inhaled allergens binding to IgE on the surface of mast cells in the skin. When the antigen bound to the IgE the mast cells degranulated releasing histamines and other inflammatory mediators that trigger swelling ,erythema, and pruritus. Scratching further damaged the skin resulting in secondary bacterial infections. Since Mast Cells were found in high concentrations on the face, pinna, and paws; itch was frequently localized to these areas, except in severe cases when itch was more generalized. This all made perfect sense. Except that we now know it isn't true (or at least most of it isn't)

What we know now

First, while the antigens are similar to those that cause allergic disease in human, the route of exposure is not inhaled, it is across this skin. This makes much more sense, but took some time and a few very cool studies to prove definitively. In both humans with atopic dermatitis (eczema) and canine patients there is a series of genetic and environmental factors that result in disruption of the epidermal barrier function. The stratum corneum and other parts of the epidermis in atopic humans is fundamentally different from that of non-atopic humans. There are proven defects in the key protein (filaggrin), the key lips (cerumides), as well as disruptions in normal keratinocyte tight junctions, maturation, differentiation, transit, and exfoliation. All of this results in a leaky barrier. This leaky epidermal barrier allows for increased transepidermal water loss, penetration of antigens deeper into the lower layers of epidermis, and increased colonization by Staphylococcus. Environmental factors such as house dust mite proteases and exfoliative exotoxins produced by Staphylococcus further the breakdown of cerumides and worsening of the epidermal barrier defect. Cool, huh?

Second, while IgE and Mast cells do play a role in inflammation in the skin, they are not as important as T-lymphocytes to the immunologic dysfunction of atopic disease. Both atopic and non-atopic dogs have two populations of T-lymphocytes (Th1 and Th2) These two population produce different cytokines in response to antigenic stimulation. Th1 cells produce cytokines we associate with good anti-viral response (Interferons), good antibacterial, antifungal, wound healing, and neutrophil/macrophage responses (IL-1, TNF-alpha) and, finally Th1 cells promote solid IgG production by B-cells. Th2 cells produce cytokines we associate with good parasite response that recruit eosinophils, upregulate mast cells, histamine release, and promote IgE production. Guess what, atopic dogs have an imbalance in Th1 and Th2, tilting dramatically towards an excess Th2 response and upregulation of eosinophils, mast cells, and IgE production.

Third, while histamine can cause vascular dilation, swelling, and erythema, it is only a mild player in pruritus in the skin. We know this intuitively because our entire careers anti-histamines have disappointed us case after case with a frustrating inability to modulate pruritus. Research into the neurologic origins of pruritus revealed a new player called IL-31. IL-31 is a cytokine that is produced by Th2 cells in the epidermis after exposure to antigenic stimulation. IL-31 and other Th2 cytokines

bind directly to unmyelinated peripheral nerves and triggers a sensation in the brain that says – scratch here. This action is mediated by a Jak-Stat pathway and is the most direct neuronal mediator of pruritus. If you inject canine Il-31 into a normal dog they will exhibit classic pruritus seen with naturally occurring atopic dermatitis. If you take a dog with naturally occurring atopic dermatitis and administer a Jak-Stat inhibitor (oclacitinib) to the dog, they stop scratcing Pfizer Animal Health (now Zoetis) developed an experimental Jak-Stat inhibitor (oclacitinib) that blocks the action of IL-31 into their new drug Apoquel.

Finally, Staphylococcus and Malassezia are not mere nuisances and flare factors that trouble allergic dogs. We now know that Staphylococcus and Malassezia contribute to the progression of atopic disease; the bacteria and yeast are inseparable from atopy. Early allergic skin and the genetic epidermal defect results in increased colonization by bacteria and yeast. The exotoxins from the organisms further lipid breakdown worsening the defect. The antigens from bacteria and yeast further stimulate the T-lymphocytes, activating danger signals within the epidermis, so that when environmental antigens from pollens, molds, housedust, housedust mites, etc are introduced the co-stimulation results in recognition of these harmless proteins as enemies by the lymphocytes. Then future exposures result in an aberrant and exhaggerated immune response to ragweed, birch, housedust mite, etc. The result is the rolling progression of worsening skin disease from a normal appearing puppy to a slightly itchy young adult with mild recurrent bacterial folliculitis, to year-round pruritus, dermatitis, and relapsing yeast and bacterial infections we recognize as Atopic Dermatitis.

Translate new findings into therapy for our patients

1. Increased focus on the epidermal barrier defect. Topical emollients and essential oils applied early on and consistently can help reduce progression of atopy in young dogs, and help repair the thickened damaged skin of older atopic patients.
2. Early recognition and aggressive intervention, management, and prevention of superficial bacterial and yeast skin infections.
3. It is not possible to over bathe allergic dogs. All of our new shampoos and conditioners are detergent free and unlikely to dry the skin. Rather, the new products all have ingredients like phytosphingosine (a procerumide) and cerumides to repair the epidermal barrier. Additionally chlorhexidine reduces both yeast and bacteria both during active infections and as a preventative between infections. Minimum of once weekly chlorhexidine will reduce the frequency and severity of future skin infections
4. Push to desensitize (immunotherapy injections) earlier in disease. I'd much rather allergy test and start immunotherapy at 1-2 years of age than 3-4 years of age. If you know what direction this is going with a young patient, start immunotherapy NOW. Antigen specific immunotherapy promotes T-regulatory lymphocytes that restore Th1 and Th2 imbalance.
5. Direct intervention of neuronal mechanism of pruritus with Apoquel can provide rapid relief from itch while managing the causes of itch. This reduces our reliance on prednisone and other glucocorticoids for symptomatic relief. Think of Apoquel as a steroid alternative that is safe for both short and long term use.
6. Atopica (cyclosporine) is predominately a T-lymphocyte modulator and is still a very safe and effective therapy with a 15 years of experience and knowledge behind it.

ACRAL LICK DERMATITIS: A NEW APPROACH TO AN OLD DISEASE

INTRODUCTION

Acral lick dermatitis (ALD) is among the top 10 most common dermatologic diseases of dogs. ALD is frustrating, expensive, miserable for the patient, responds poorly to therapy, and reoccurs frequently. Therapeutic success rates ranges from 20-65%, including unusual treatments, like intralesional Cobra venom. In spite of this, there is remarkably little clinical research performed to improve understanding of the pathogenesis of ALD.

CLINICAL PRESENTATION

ALD is characterized by self-traumatizing licking that results in progressive development of well-circumscribed, firm, proliferative, erosive/ulcerative, alopecic plaques or nodules on the lower portion

of the limb. While appearance and size can be quite variable, the consistent feature recognized by veterinarians and owners is excessive licking. Lesions are usually found on the dorsal aspect of the carpus, occasionally extending down the metacarpus, or up to the elbow. Less commonly the lateral tarsus or metatarsus is involved. A recent survey, demonstrated front limb only involvement in 21 of 31 dogs (68%), front and hind limb involvement in an additional 6 of 31 (19%), and hind limb only involvement in only 4 of 31 (13%). Lesions are often painful with patients resisting manipulation or palpation; some dogs demonstrate lameness or decreased activity. Any breed can be affected, but there is a predisposition for large breed dogs with short coats: Doberman Pinscher, Great Dane, Labrador Retriever, Boxer, and Weimaraner. Other frequently mentioned breeds are German Shephard, Golden Retriever, and Irish Setter. A common theme is relatively short hair on the dorsal aspect of the limbs. Median age of onset is 4 years (range 1 – 12 years).

CAUSE

Etiology of ALD is complex and multifactorial. To simplify understanding, all causes and contributing factors can be divided into three categories: (1) predisposing, (2) primary, and (3) perpetuating factors.

Table: Multifactorial causes of canine acral lick granuloma

Predisposing	Primary	Perpetuating
Large Breed Dog	**Food Allergy**	**Deep bacterial infection**
Short Hair Coat	**Atopic Dermatitis**	**Pain**
Not walked at all	Orthopedic / Spinal	Entrapped free hair shafts
Housed outdoor only	Trauma	Apocrine gland inflammation
Concurrent Behavior Problems	Neoplasia	Fibrosis
	Fungal infection	Reinforced behavior
	Foreign Body	
	Parasthesia / Neuopathy	
	Behavior Disorders	

Predisposing factors are things that do not directly cause ALD but make initiation and progression of ALD more likely. This includes breed predisposition and short hair coat over affected limbs. One recent study, suggested an increase risk for ALD in dogs that were rarely or never taken for walks, dogs that were housed outdoors only.

Primary causes are conditions that initiate licking at the target site, setting up progression of changes that result in clinical lesions. Foremost among these are diseases that cause pruritus: food allergy and atopy. Less common causes include trauma, neoplasia, dermatophytosis, foreign body, osteoarthritis, parasthesia, neuropathy, and behavior disorder. A recent case series reported clinical lesions, resulting from a Kirshner pin, lymphoma, mast cell tumor, sporotrichosis and Leishmania. Behavior is often described as the most common cause for canine ALD. In our clinic, food allergy is the most common, followed by atopy; all other causes are rare, including behavior. In cases with a final diagnosis of primary behavior disorder, patients exhibited multiple behavioral problems; including, separation anxiety, phobia, or other stereotypic behavior, such as tail-chasing, circling, wool sucking, fly biting, or rhythmic barking. If a dog with ALD presents with additional behavior problems, then suspect a primary behavior cause; however, in the absence of concurrent behavioral disorders, pursue food allergy, atopy, and other diseases first, while addressing behavior as a perpetuating factor.

Collaborative prospective studies with both dermatology and behavioral specialties need to be performed to better determine etiology and characteristics of primary behavioral ALD. A good model is a recent study of another “behavioral” dermatosis, psychogenic alopecia. This study evaluated 21 adult cats referred with a presumptive diagnosis of psychogenic alopecia; in 19 cats a primary pruritic disease was identified, with only 2 cats found to have a psychogenic cause. Food allergy was the most common diagnosis, confirmed in 12 of 21 cats. Like “psychogenic” alopecia, a behavioral cause for ALD should only be diagnosed when all causes of pruritus have been eliminated.

Perpetuating factors are conditions that result from licking and progress to an amplifying cycle of self-traumatic licking. The three most common perpetuating factors are (1) deep bacterial infection, (2) free keratin debris and subsequent pain and inflammation, and (3) behavior. In a recent prospective study, deep tissue bacterial infection was identified in 29 of 31 dogs (94%). One dog was culture

positive for *Microsporum gypseum*. The most common deep tissue isolates were *Staphylococcus* (58%), *Pseudomonas* (8%), and *Enterobacter* (8%). Antibiotic resistance was unpredictable; 52% of isolates were resistant to three or more antibiotic drug classes commonly used for Staphylococcal pyoderma (cephalosporin, clindamycin, potentiated sulfonamides, amoxicillin/clavulanate , and fluoroquinolones). Methicillin-resistant *Staphylococcus* was isolated in 25% of cases. Surface culture was a poor predictor of deep isolates; therefore antibiotic selection should be based on culture obtained by biopsy or purulent exudates squeezed from deep in the lesion.

Another major cause for progression and perpetuation of the self-traumatizing lick is ruptured hair follicles, free hair shafts, and inflammatory response to keratin. Dogs start licking as a manifestation of pruritus, which may result in focal bacterial folliculitis, which is pruritic and stimulates more licking. In short-coated breeds, licking results in rupture of hair follicles and forcing of short, stiff hairs into the deep dermis. Keratin is phenomenally irritating to tissues and elicits a profound acute and chronic inflammation. Hair shaft foreign bodies are very painful and elicit continued licking. Over time, these changes progress to commonly described histopathologic features of ALD: ulceration, dermal fibrosis with a vertical streaking pattern, thickened and elongated hair follicles, free hair shafts, and diffuse pyogranulomatous to lymphocytic-plasmocytic inflammation In the prospective study of 31 dogs, epitrichial sweat glands were also found to be heavily involved, exhibiting periglandular inflammation (90%), hypertrophy (81%), inspissation (81%), dilation (71%), severe focal inflammation in the glands (hidradenitis; 29%) and glandular rupture with secretions free in the tissue (10%). The role of epitrichial gland inflammation in the progression of ALD is unknown, but histopathologic changes are similar to proliferative end-stage (cauliflower) otitis in Cocker Spaniel dogs.

Behavior is more likely involved in progression and perpetuation of canine ALD rather than as a primary cause. Repetitive, “compulsive” licking in ALD has been compared to obsessive-compulsive disorder (OCD) in humans. While very little is known about neurophysiology and neurochemistry of dogs with ALD, humans have been studied extensively. Some human patients have abnormal neural pathway between the frontal lobes (consciousness and perception) and the caudate lobe of the basal ganglia (planning and execution of movements). As a result OCD patients demonstrate recurrent impulsive repetitive behaviors, such as hair pulling (trichotillomania), hand-washing, checking of lights, stoves, door locks, unplugged irons; the patient is consciously aware they just washed their hands, but the information that the action is completed and no longer needs to be done does not get processed properly and the patient repeats the behavior. This may be true in dogs with some stereotypic behaviors, but seems unlikely in ALD. Do dogs think “I just licked my paw, my paw needs licking?” In addition to neural pathway disorders, humans with OCD have low serotonin activity. Serotonin is a vital neuromodulator involved in nearly every aspect of behavior, response, and action. Repetitive motor activities in OCD patients increase serotonin activity, creating a self-medicating feedback loop that reinforces the behavior. Dogs with ALD may also experience reinforced feedback, where licking provides both a temporary alteration of local sensation (relief of pain/pruritus) and pleasurable increase in serotonin activity in the CNS. Partial clinical improvement with Selective Serotonin Reuptake Inhibitors (SSRI) supports this observation

DIAGNOSIS

Diagnosis should focus on both primary cause and perpetuating factors. Use both dermatology and behavior history questionnaires to assist in early identification allergic or behavior disorders. Any pruritus or otitis? Think allergy; however, do not rule out allergy if ALD is the only manifestation of pruritus. If behavioral history shows concurrent anxiety, phobia, or stereotypic behaviors, then more aggressive pursuit of behavior is warranted. In most cases, think food or atopy first, not behavior.

The initial minimum database should include, cytology, skin scrape for demodicosis, and dermatophyte culture. Documentation of the size and appearance of the lesion with digital photography, calipers, or tracing of the lesion through clear acetate is important for later comparison.

Biopsy for histopathologic confirmation and bacterial culture and sensitivity is also recommended. Histopathology is the most direct method for ruling out organic causes such as neoplasia or deep mycosis. Of greater value is deep tissue culture and sensitivity. 95% of dogs with ALD have deep pyoderma, and most have bacteria with unpredictable susceptibility to antibiotics. Since ALD may require prolonged treatment (2-6 months), antibiotic selection based on culture increases the

opportunity for success. Surface swabs show oral contaminants or more routine surface bacteria. My method is sedation with IV medetomidine at 5-8 ug/kg and butorphenol 0.2mg/kg followed by local anesthetic block. Lidocaine is administered subcutaneously in a semi-circle proximal and under the lesion. Injections into the lesion may disrupt the dermal architecture and inhibit bacterial growth. If necessary, intravenous propofol can be administered to effect; however, propofol provides no analgesic activity. Use surgical scrub and aseptic surgical technique. With a sharp (new) 6mm punch biopsy collect a deep biopsy from the center of the lesion; with a scalpel blade, trim the epidermis from the dermis and submit only deep tissue for culture. If unable to biopsy, sample deep exudate by squeezing the lesion until a small quantity of exudate emerges from a follicular pore.

Elimination diet trial is an essential test for canine ALD. Following 8-12 week trial, ask – is the dog licking less and is the lesion smaller. The answer may be yes because of resolution of infection; therefore the true diagnostic test is provocative challenge with the original diet. Intradermal allergy testing or allergy serology to identify allergens for inclusion in allergen specific immunotherapy is indicated in any patient that fails to respond to elimination diet trial. Radiography of the affected limb may be helpful to evaluate for underlying osteoarthritis, implants, neoplasia, or deep mycotic infection. In chronic ALD, the presence of periosteal reaction on radiograph is a negative prognostic factor.

THREE PRONGED APPROACH TO THERAPY

Focus on **THREE** key components: (1) Pain Management, (2) Effective Antibiotic Therapy, and (3) Management of Primary Disease, failure in any one of these areas will likely result in poor response, recurrence, or progression.

Pain is perhaps the most underappreciated and therefore undermanaged perpetuating condition in ALD. Pain can occur from entrapped hair shafts and deep pyoderma can be a major factor that stimulates continued “compulsive” licking. Additionally orthopedic or neuropathic pain may be the primary or initiating reason. Use of analgesics such as non-steroidal anti-inflammatory drugs is the first line of therapy. Adjunctive therapy with gabapentin and/or amantadine may be useful, but has not been thoroughly researched. Gabapentin is an antiepileptic drug with utility in managing neuropathic pain. Amantadine is an NMDA receptor antagonist. Check with your local anesthesiologist for dosing guidance as ideal dosages have not been determined for Gabapentin or Amantadine in dogs.

Managing the deep bacterial infection requires a safe, effective, and convenient antibiotic that the owners and the animal can tolerate for a protracted periods. Because resistant bacteria are common, and because the owner will be administering oral antibiotics for prolonged courses, try to choose an effective antibiotic based on susceptibility profile that is administered easily, on a simple schedule. cefpodoxime or ormethoprim sulfadimethoxine one time daily is ideal for susceptible bacteria. Once daily fluoroquinolones marbofloxacin and enrofloxacin can be used for gram-negative infections where no other oral choice is rationale. Use the highest achievable dose or combining with a second antibiotic to minimize risk of developing resistant strains. Other choices based on culture can include cephalosporins, clindamycin, chloramphenicol, doxycycline, and amoxicillin/clavulanate. Always aim high with dose and duration, as relapse and failure are common.

Topical mupirocin ointment is excellent for *Staphylococcus*, including methicillin-resistant strains. Topical benzoyl peroxide gels and washes can be beneficial as a superficial antiseptic and to open hair follicles and facilitate removal of keratin debris. Epsom salt soaks may help. Other topical therapies with variable utility and efficacy include, fluocinolone and DMSO, flunixin meglamine, and capsaicin. A mixture of 1/3 liquid HEET and 2/3 Bitter Apple has also been described. Use caution with any topical therapy if therapy directs the dog’s attention to the area, causing increased licking rather than less. Ideally apply topicals then distract the dog.

Other treatments including therapeutic laser, surgery, cryotherapy, surgical laser ablation, radiation therapy, and acupuncture have been reported with variable success. I prefer to use laser ablation only after the primary disease is diagnosed and managed and antibiotics have been administered to maximal benefit. Patience is necessary; the remaining lesion is smaller, and contains only fibrosis, trapped hair shafts, and foci of bacteria. Manage as any open wound healing by second intention; prevent continued licking.

Treatment of primary allergic disease may include diet, allergen immunotherapy, cyclosporine (Atopica, Novartis), and short courses of steroids to break the itch-lick cycle. Use corticosteroid doses and protocols employed for routine atopic dermatitis; avoid higher, longer, or aggressive steroid usage simply because ALD is a more severe. Previous poor response to corticosteroids is probably due to deep pyoderma not insufficient steroids. High steroid doses are not more likely to resolve bacterial infection than low doses. Intralesional steroids will prolong infection and ALD.

Behavioral therapy is focused on two areas – behavior modification and drugs. Seek expert advice for effective protocols for concurrent behavioral diagnosis (separation anxiety, phobia, or stereotypic behaviors). Behavior modification therapy may include avoidance of recognized triggers, counter-conditioning, and distraction techniques, such as social and environmental stimulation, exercise, and increased play. Aversion therapy with shock collars was reported to be beneficial in 4 of 5 cases. However, guidance from an experienced behaviorist is strongly recommended before using this therapy. Aversion is one of the hardest behavior modification techniques to apply effectively; 100% application of the stimulus is required; partial or intermittent application can actually reinforce the behavior rather than extinguishing it. Also aversive stimuli does very little to resolve pruritus or pain associated with impacted hair shafts and deep pyoderma. Drug therapy may help resolve perpetuating, self-medicating serotonin feedback loop; consider tricyclic antidepressant: clomipramine and Selective Serotonin Reuptake Inhibitor: fluoxetine hydrochloride.

Bandaging, using E-collars, muzzles, and other techniques to physically restrain the dog and preventing licking meets with mixed results. Early on in the management restraint may actually be counterproductive, as pain and pruritus are usually very high and the motivation to lick is powerful. Some dogs will resort to self-destructive licking around the restrains or at other limbs, resulting in worse disease not better. I prefer to wait until the lesion is improving and stimulus is reduced before attempting restraint. I will definitely use restraint following laser ablation or other surgical intervention.
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SUMMARY

- ALD is a multifactorial disease with predisposing, primary, and perpetuating factors
- Pain-management is an important component of therapy
- 95% of acral lick lesions have deep bacterial infections
- Bacterial infection is less predictable than routine pyoderma
- Culture by biopsy or by squeezing up deep exudates
- Most dogs with primary behavior ALD exhibit other behavior problems

SUGGESTED READING

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