Recognition and Management of Allergic Patients

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Abstract: Pets commonly present to veterinarians for management of pruritus (itch), skin infections and otitis. These complaints are usually secondary to an underlying allergic disease. History, physical exam and response to medications help narrow down the type of allergy (atopy, food, flea or contact). This presentation will describe the six options that dermatologists employ to manage atopy and the mechanisms of action: antihistamines combined with essential fatty acids, steroids, allergen specific immunotherapy (ASIT)--delivered by subcutaneous injection or sublingual drops, steroids, cyclosporine, oclacitinib and lokivetmab.

Keywords: folliculitis, pruritus, atopy, antigen-presenting cell, cytokine

The skin not only keeps the outside out and the insides in but has many other functions. It gives motion and shape to the body it covers, produces Vitamin D, and acts as a storage center (water, fat) but also has secretion and excretion functions. It allows sensation of touch and protects the body from infection. The skin is an indicator of general health. An example of this is jaundiced skin which should trigger assessment of the patient for liver disease. For our furry allergic patients, it is sometimes difficult to see abnormal changes to the skin until they exhibit itching and/or signs of folliculitis.

There are four types of allergy: contact, flea, food and atopy (environmental allergies). Contact allergy is uncommon and in our pets is exhibited in areas that are typically sparsely haired such

as the belly region. Direct contact with the offending allergen is required for this type of allergy to occur.

Flea allergy dermatitis is very common, particularly in the south, and occurs year round. Fleas are most prolific when the temperature and humidity are around 70 for each (degrees Fahrenheit and % humidity). In dogs, the classic distribution pattern is the caudal dorsum/tail head however, flea allergy dermatitis should be included on the differential list when back half of the body pruritus is noted (belly, inguinal region). For cats, distribution of pruritus for flea allergy is also the back half of the body but when miliary dermatitis (crusted papules—often palpated rather than seen) is noted anywhere on the body, flea allergy should be suspected and flea control should be instituted. Folliculitis (alopecia, papules, pustules, crusts, epidermal collarettes) commonly accompanies flea allergy dermatitis in dogs and the differential list should now also include bacteria, *Demodex* and dermatophyte. Pyoderma is the most common culprit in this situation and antibiotics (systemic and/or topical) along with aggressive flea control and antipruritic medications are necessary.

Food allergy (hypersensitivity) may occur with any food ingredient or a food additive. The distribution pattern of pruritus includes the face, ears, ventrum and paws and itch is generally intense and steroid non-responsive to minimally responsive. Oral allergy (rubbing the face/muzzle) after eating may also be noted. Food hypersensitivity can occur at any age regardless of the quality of diet of fed but is most common in young (<6 months) and older (>7 years) animals. It should be higher on the differential list in those less than one year old in areas that have distinct seasons. If 6 months old or less, a food trial should be instituted. In older animals, the usual presentation is acute, intense pruritus but an additional differential of cutaneous lymphoma would now be considered in this patient.

Atopy is Greek for “strange disease”. Environmental allergies to pollens such as grasses, weeds, trees, molds, and other allergens like house dust and house dust mite are responsible for causing atopy or atopic dermatitis. Patients with atopy generally present with their first skin issues beginning between 6 months and 6 years with one to three years being the classic age of onset. The distribution pattern of pruritus includes the face, ears, ventrum and paws but is usually very steroid responsive. Every year upon re-exposure to seasonal allergens, the severity of the allergic reaction becomes more and more exaggerated eventually leading to secondary skin infections which also add to the pet’s pruritus and discomfort. In the south, it may be trickier to establish seasonality patterns due to mild winters. Terriers, retrievers and bulldogs tend to be predisposed but any and all breeds or crosses may be allergic. Patients presenting for recheck exams regarding pruritus should be investigated for secondary infections. Many antipruritic therapies may seem to be ineffective but the pruritus is from the secondary infection infections.

There are 6 treatment options for atopic dermatitis: antihistamine +/- essential fatty acids, steroids, cyclosporine, oclacitinib, lokivetmab and ASIT. Topical medication such as shampoo, mousse, wipes and spray are often used in conjunction with these therapies. The treatment options recommended work on different parts of the immune system and when considering therapy, a full medical history is important as some drugs may be contraindicated in some patients. The ideal therapeutic options would ideally stop the neuronal itch stimulation and halt inflammation without causing side effects. It is often necessary to combine these therapies indefinitely or on an as needed basis during seasonal exacerbation. The goal when managing allergies in patients is to decrease the severity of pruritus by 80-90% about 80-90% of the time. When on immunosuppressive medications (steroid, oclacitinib, cyclosporine) that carry adverse

side effects tapering to the lowest effective dose is necessary. Lowest effective dose does not mean zero itch all the time which is important from a communication standpoint.

How allergens affect and interact with the immune system is complex and research continues on shaping thoughts and theories on the entire process. This research has led to newer more targeted therapeutic choices.

To understand how these treatments work, a review of what happens in the body at a cellular level may be helpful. The most recent research supports that the offending pollen or allergen comes into contact with the skin and is absorbed percutaneously across defects in the skin barrier. Antigen presenting cells (APC) are found within the epidermis and engulf the allergens. The APC then migrate down into the dermis and then into a regional lymph node. T-cell lymphocytes are then activated to release cytokines, particularly IL-4 & IL-13. Some cytokines stimulate B-cell lymphocytes to release allergen specific immunoglobulin E (IgE) antibodies. Other cytokines activate mast cell degranulation releasing histamine. The activated T-cells come out of the lymphatic system and migrate back to the dermal layer of the skin. Once there, the T-cells release cytokines which allows a continuous cycle of inflammation and pruritus.

Now that the immune cells have been sensitized, they are primed. Now the APC rapidly recognizes the offending allergen triggering activation of the T-cell which produce the pruritogenic cytokine IL-31. IL-31 travels and binds to receptors on the surface of neurons. This is one way that can trigger the activation of Janus Kinase pathway (JAK). JAK can stimulate a signal along the nerves to the brain which promotes the itch response to specific allergens.

Inflammation is a big factor in the development of skin disease and occurs when certain cytokines from T-cells are released. Allergens bind and crosslink to IgE antibodies on the

surface of mast cells causing the mast cell to release more pro-inflammatory cytokines including histamine. Pro-inflammatory cytokines recruit other inflammatory cells such as eosinophils and neutrophils from the blood to the dermis leading to expansion of activating more JAK pathways. This results in inflammation of the skin appearing as erythema, or redness. More cytokines are released affecting the skins barrier function which in turn stimulates the neural itch.

The first therapy often implemented at the first signs of pruritus are antihistamines. Antihistamines work by stopping mast cells from releasing histamine. However, mast cells also release cytokines, prostaglandins, leukotrienes and kinins. There are several over the counter and prescription options and while one may work well in one patient, it may not work as well for another and a trial with a different types may be needed to find one that is effective for that patient as well as have minimal sedative effects. When the pruritus level is high, a significant reduction in pruritus is not likely. Ideally, essential fatty acids (EFA) with high concentration of eicosapentaenoic acid (EPA) are used in combination with antihistamines. EFA's have an anti-inflammatory effect to help decrease pruritus as well as have a synergistic effect with the antihistamine enhancing its effectiveness. Additionally, EFA's provide building blocks to help repair defects in the skin barrier secondary to allergies and inflammation and improve coat quality.

Glucocorticoids reduce inflammation and related pruritus and are very effective but they have non-target effects on the liver, kidneys and adrenal glands as they affect all cells. The steroid binds to glucocorticoid receptors in the cell and then translocates to the nucleus. The steroid prevents inflammation by controlling the rate of protein synthesis by either blocking the action of inflammatory mediators or by inducing anti-inflammatory mediators and suppressing migration of neutrophils.

Allergen specific immunotherapy (ASIT) is considered the gold standard for the treatment of atopy. Allergy testing is performed by intradermal (gold standard) or by serology. Interpretation of the results with consideration to the patient's allergy history is necessary to formulate a unique therapy solution for each individual. This therapy retrains the immune system to be more tolerant to the allergens the patient is sensitive to.

Cyclosporine is used for treating allergies and immune mediated diseases. Allergens bind to receptors on the T-cells causing the calcium within the cell to increase and activates calcineurin production. Cyclosporine inhibits calcineurin production and interferes with the cell's ability to produce cytokines, particularly interleukin 2 (IL-2) that causes activation and proliferation of T-cells.

Oclacitinib works on the JAK pathway that is responsible for activating the cascade which creates an allergic response. A cytokine binds to the JAK receptor like a lock and key and this triggers production of JAK enzymes. Oclacitinib blocks the JAK pathway enzymes from being synthesized, therefore blocking the allergic response from occurring.

Lokivetmab is an antibody that binds up and neutralizes IL-31 before it binds to a receptor. This also means the itch signal is never sent as IL-31 isn't present to bind to the receptor. In other words, the lokivetmab stops the chain of events before able to get started.

Lastly, instituting topical therapies available in a variety of preparations will enhance the control and management of allergies. Secondary infections (bacteria, yeast) affect approximately two-thirds of atopic patients. These therapies have active ingredients that will treat active infections as well as act as keep normal skin flora controlled to keep infection at bay. Active ingredients such as ceramides and phytosphingosine are included in many formulations to help repair the

skin barrier reducing the allergen's ability to reach the APCs in the epidermis. Mechanical removal of pollens on the coat and hair will decrease the patient's exposure to the allergens.

In summary, allergic patients need consistent management from the owner as well as the veterinarian. Many patients require multiple therapies concurrently to achieve control of atopy and pruritus. These patients will itch, will flare and will likely get infections. Rule out and treat the simple (infections), continue year round flea control (if evidence of flea allergy, CHANGE the flea control), and lastly, ask the pet owner if the current therapy to control the allergies is working. If not, additional differentials may need to be ruled out if not explained by presence of infection or CHANGE the therapy.

References:

Miller WH, Griffin CE, Campbell KL. Small Animal Dermatology, 7th ed. St. Louis, MO. Elsevier. Muller & Kirk. 2013

Hnilica, KA, Patterson AP. Small Animal Dermatology, A Color Atlas and Therapeutic Guide, 4th ed. St. Louis, MO. Elsevier. 2017

Tizard, I. Veterinary Immunology, 10th ed. St. Louis, MO. Elsevier. 2018

Hicks, Karly "The Solution to Pruritus", Auburn University

White, Amelia "A Scratch for Every Itch", Auburn University

Zoetis: www.zoetisus.com/conditions/dogs/itchcycle/home.aspx