When, Why, and How - Making the Most of the Diet Trial as a Diagnostic Test

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The classifications of adverse reactions to food can be either immunologic or non-immunologic. Food allergy is defined as any immune-mediated reaction occurring after food intake. This can be either IgE-mediated (immediate) or non-IgE mediated (delayed). Examples of non-immunologic adverse food reactions include poisoning, metabolic reactions, or anaphylactoid responses. For our purposes, we will review immunologic reactions to food in the dog and cat and focus on making an accurate diagnosis of this condition.

Pathogenesis

The digestive tract is responsible for differentiating between nutrients and harmful substances each and every time a food item is consumed. The ability of the body to maintain homeostasis in the face of exposure is called tolerance. In order for tolerance to be achieved, the gut must maintain an intact mucosal barrier, regulate the immune response, eliminate antigens appropriately, and generate a system of tolerance for antigens. The Gut Associated Lymphoid Tissue (GALT) is composed of four distinct compartments of lymphocytes. Each provide the surveillance and response capacity necessary to operate a fully functional gastrointestinal barrier between what we consume and what we absorb.

The rate of intact protein absorption through the mucosal barrier of the gastrointestinal tract (GIT) will depend on many factors. First, enterocytes must have normal morphology and functionality. If the cells of the barrier are not normal or functioning appropriately, the barrier is defunct. Second, IgA must be present in order to appropriately bind and remove antigens. IgA serves as a marker for antigens and helps aid in their homeostatic elimination. Third, digestion need be complete to aid in the processing of food into smaller, less antigenic molecules. Complications after surgery or comorbidities that impact digestion could play a role in the barrier function of the GIT. Similarly, food composition plays a role. If food is easily digestible, there will be less risk of intact, large protein absorption. And, finally, the presence of inflammation will impact the stability of the barrier. Inflammation begets inflammation.

If an antigen is something considered as foreign to the body that induces an immune response, what exactly is a "food antigen"? Technically, all food is potentially antigenic since it is foreign and has potential to initiate an immune response. Food is made up of complex matrices of natural constituents such as proteins, fats, and carbohydrates. As the body digests food, by-products of the original food structure are created. Fats are metabolized into fatty acids. Carbohydrates are broken down into sugar molecules. Proteins are digested into amino acids and small peptides.

Most antigens are proteins. They are composed of amino acid chains that have numerous unique structures called epitopes. These regions are the exact recognition sites that a specific immunoglobulin molecule would bind to. The larger the protein, the more epitopes. The less digestible the protein, the larger it will be. The more epitopes and the less digestible, the more antigenic.

When you combine poor barrier function, altered self-regulation, reduced elimination of antigens, and a lack of tolerance – you are left with the potential for an allergic cascade. Notice that this classification could be considered for any barrier – skin or gastrointestinal.

The allergic cascade is perpetuated by a shift from a tolerant phenotype to an intolerant one. As tolerance is lost, the predominant immunoglobulin shifts from IgA to IgE. Type 1 hypersensitivity reactions are driven by antigen binding which leads to IgE cross-linking and histamine release from mast cells. The result – inflammation. This translates clinically into vomiting, diarrhea, and other clinical signs. While we do not believe that all food allergy in dogs and cats is mediated by Type 1 hypersensitivity reactions, we do believe that IgE sensitization plays an important role. Type I, Type III, and Type IV hypersensitivity reactions are likely part of the immunologic basis of food allergy in the dog.

Inflammation driven by IgE and histamine release further weakens the mucosal barrier's integrity. This leads to more intact protein molecules being absorbed and additional sensitization of new proteins. Furthermore, if the gut is broken down, and antigens travel through the blood stream, mast cells bearing IgE in the skin or sensitized basophils in the blood can be activated. This can lead to cutaneous clinical symptoms and is the presumed pathomechanism of cutaneous adverse food reaction in the dog.

Food Allergy Stats – Dogs and Cats

The prevalence of cutaneous adverse food reaction in dogs and cats was found to vary depending on the type of diagnosis made. This is a major issue regarding our understanding of this condition. Accurate diagnosis of food allergy in the dog and cat is plagued by issues of compliance and variability in administration and interpretation. Regardless, 1-2% of dogs who presented to their veterinarian for any diagnosis were found to have food allergy. Dogs with skin disease: 0-24%, dogs with pruritus: 9-40%, any type of allergic skin disease: 8-62%, dogs diagnosed with atopic dermatitis: 9-50%. The take home here is that about 25% of your allergic patients are food allergic.

Dogs and cats with food allergy have similar cutaneous symptoms which can vary in severity and presentation. Age of onset tends to be young (< 1 year of age; noted in 22-38% of dogs). All have a non-seasonal, continuous pruritus.

There is no sex predilection and breed is unlikely to matter overall. Pruritus is often generalized. However, special attention should be paid to perianal pruritus as this is much more commonly linked with food allergy than environmentally triggered atopic dermatitis. Other secondary symptoms to be aware of include otitis externa, recurrent pyoderma, and atopic clinical signs. Similarly, in cats, symmetric self-induced alopecia, head-and-neck self-traumatic dermatitis, military dermatitis, and variants of eosinophilic diseases are the most common manifestations of feline cutaneous adverse food reactions.

Extracutaneous signs are also essential to recognize. For example, dogs with cutaneous adverse food reaction also tend to have gastrointestinal signs manifesting as vomiting, diarrhea or soft stool, increased frequency of defecation, and anal gland pathology. It is important to ask about the fecal quality and frequency using a visual aid when talking with owners about this aspect of their pet's health. Over 85% of healthy dogs are not described as pruritic (PVAS < 2), have a fecal consistency score of 2-3 (94.9%) and have 1-2 bowel movements per day (96%). Very often, allergic patients do not meet these criteria; food allergy should be suspected.

Food Allergy - Diagnosis

There is only one test to diagnose adverse food reaction in the dog (or cat) and that is an elimination diet trial with a prescription or home cooked diet that is made from a novel protein and carbohydrate. Serum tests for food-specific IgE and IgG, intradermal testing with food antigens, lymphocyte proliferation tests, fecal food-specific IgE, patch, gastroscopic, and colonoscopic testing have been evaluated. In general, these tests have low repeatability and accuracy. The only test recommended for the diagnosis of food allergy in the dog is the elimination diet trial.

The ideal composition of a diet used to diagnose food allergy in the dog or cat has many components. Simply, the diet should be one that the patient was not previously exposed to, has a limited number of new, highly digestible proteins OR is a hydrolyzed protein, contains a lower protein content and additives, and is nutritionally adequate for the life-stage of the patient. Choices include home cooked diets that contain a novel protein and carbohydrate, commercial novel protein diets, and commercial hydrolyzed protein diets.

At this time, there are concerns regarding the use of home cooked diets and commercially prepared novel protein diets for the purposes of diagnosing food allergy in the dog or cat. Home cooked diets are poorly balanced and can be quite costly to prepare. While a commercial novel protein diet is balanced, they are not currently recommended for use for diagnosing food allergy due to their variable efficacy and concerns with cross-reactivity.

Cross-reactivity occurs when proteins in one substance are like proteins in another. The immune response that is generated is the same or similar when exposure of one or the other occurs. This can happen between foods, between foods and environmental triggers, or between environmental triggers. An example includes cross-reactivity between chicken and crocodile protein leading to anaphylaxis in a chicken allergic child. We have limited understanding of this in our veterinary patients. However, enough is known in human medicine to generate pause when using these diets for diagnostic purposes.

Commercial hydrolyzed protein diets subvert concerns of cross-reactivity via hydrolysis. This process reduces whole proteins to smaller peptides and amino acids. Molecular weight is reduced and epitopes are disturbed. As a result, IgE cross-linking is prevented and allergic response is much less likely. These diets are also nutritionally complete for various life stages. My current recommendation for a diagnostic diet for food allergy is an extensively hydrolyzed, commercially prepared food that is nutritionally balanced for the patient's life stage.

The diet trial should last 8 weeks. This has been shown to be an adequate amount of time to identify over 90% of food allergic patients. Interestingly, gastrointestinal signs tend to clear up within 2-3 weeks of starting an exclusively fed commercial hydrolyzed protein diet. This is often a first marker for me to determine if the diet will be useful from a diagnostic perspective. If GI signs have not resolved within the first two weeks, consider a different diet for your diet trial.

Interpreting the diet trial involves demonstrating a reduction in pruritus and a resolution in other clinical signs. This can be complicated if there are treatments on board which could mask symptoms, infection present that has not been adequately treated, or partial responses due to the ebb and flow of environmental allergy. In the end, it is important to remember that a diet is a benign, conservative strategy which can drastically improve the health and life quality of an allergic patient. Continuing the diet past the 8-week period to sort these potential complicating factors out is usually well worth it. However, this should always be done deliberately to avoid having your patient on a diet that is medically unnecessary.

Confirming your diagnosis of food allergy involves an oral food challenge. There are many ways to perform dietary challenges. My recommendation is to tailor all "life after the diet trial" steps to your individual patient and client. Nevertheless, it is important to know that it can take up to 14 days for a dog to show clinical flare after an oral food challenge; cats can take up to 7 days. Therefore, all challenges should be spaced out accordingly.

Communication about the diet trial should be direct and informative. In order to improve adherence to diet trial recommendations, veterinarians should improve knowledge, reduce perception of barriers, and heighten self-efficacy (owner confidence). This is one of the few diagnostic tests that is left in the hands of a pet owner. We need to improve our communication about this test in order to improve our diagnostic outcomes. Improving health outcomes through communication is a goal that we all strive for and that is especially the case when it comes to the diet trial and food allergy.

References

A. Verlinden , M. Hesta , S. Millet & G. P.J. Janssens (2006) Food Allergy in Dogs and Cats: A Review, Critical Reviews in Food Science and Nutrition, 46:3, 259-273.

Olivry, T., Mueller, R.S. & Prélaud, P. Critically appraised topic on adverse food reactions of companion animals (1): duration of elimination diets. *BMC Vet Res* 11, 225 (2015). https://doi.org/10.1186/s12917-015-0541-3

Olivry, T., Mueller, R.S. Critically appraised topic on adverse food reactions of companion animals (3): prevalence of cutaneous adverse food reactions in dogs and cats. *BMC Vet Res* 13, 51 (2016). https://doi.org/10.1186/s12917-017-0973-z

Mueller, R.S., Olivry, T. Critically appraised topic on adverse food reactions of companion animals (4): can we diagnose adverse food reactions in dogs and cats with in vivo or in vitro tests?. *BMC Vet Res* 13, 275 (2017). https://doi.org/10.1186/s12917-017-1142-0

Mueller, R.S., Olivry, T. Critically appraised topic on adverse food reactions of companion animals (6): prevalence of noncutaneous manifestations of adverse food reactions in dogs and cats. *BMC Vet Res* 14, 341 (2018). https://doi.org/10.1186/s12917-018-1656-0

Olivry, T., Mueller, R.S. Critically appraised topic on adverse food reactions of companion animals (7): signalment and cutaneous manifestations of dogs and cats with adverse food reactions. *BMC Vet Res* 15, 140 (2019). https://doi.org/10.1186/s12917-019-1880-2

Olivry, T., Mueller, R.S. Critically appraised topic on adverse food reactions of companion animals (9): time to flare of cutaneous signs after a dietary challenge in dogs and cats with food allergies. *BMC Vet Res* 16, 158 (2020). https://doi.org/10.1186/s12917-020-02379-3