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Comparing immediate type food allergy in humans and companion animals – revealing unmet needs

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Abbreviations

AAI, alpha-amylase inhibitor

ACE I, angiotensin-I-converting enzyme

AD, atopic dermatitis

AE, angioedema

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AFR, adverse food reactions

APC, antigen-presenting cell

AP-N, aminopeptidase N

APT, atopy patch testing

AU, acute urticaria

CADESI-04, Canine Atopic Dermatitis Extent and Severity Index

DBPCFC, double blind placebo-controlled food challenge

EPIT, epicutaneous immunotherapy

IDT, intradermal testing

IL, interleukin

LMW, low molecular weight

NHANES, National Health and Nutrition Examination Survey

nsLTP, non-specific lipid transfer protein

OAS, oral allergy syndrome

OFC, oral food challenge

OIT, oral immunotherapy

PR-10, pathogenesis-related proteins class 10

SCIT, subcutaneous immunotherapy

SLIT, sublingual immunotherapy

Treg, T-regulatory cells

Abstract

Adverse food reactions occur in human as well as veterinary patients and systematic comparison may lead to improved recommendations for prevention and treatment in both. In this position paper, we summarize the current knowledge on immediate type food allergy versus other food-adverse reactions in companion animals, and compare this to the human situation. While the prevalence of food allergy in humans has been well studied for some allergens, this remains to be investigated for animal patients, where owner-reported as well as veterinarian-diagnosed food adverse reactions are on the increase. The characteristics of the disease in humans versus dogs, cats, and horses are most often caused by similar, but sometimes species-dependent different, pathophysiological mechanisms, prompting the specific clinical symptoms, diagnoses and treatments. Furthermore, little is known about the allergen molecules causative for type I food allergy in animals which, like in human patients, could represent predictive biomarkers for risk evaluation. The definite diagnosis of food allergy relies -as in humans- on elimination diet and provocation tests. Besides allergen avoidance in daily practice, novel treatment options and tolerization strategies are underway.

Taken together, numerous knowledge gaps were identified in veterinary food allergy, which need to be filled by systematic comparative studies.

Introduction

Adverse food reactions (AFR) encompass food intolerances as well as immunologically mediated hypersensitivities, i.e. food allergies. They may occur in human as well as in veterinary patients. As there is no cure for food allergy today, it is of utmost importance to identify the causative allergens and pathophysiological mechanisms, and to develop adequate preventive measures and treatment strategies.

Various animal species have been used to study mechanisms of food allergy or the allergenic potency of novel foods (1). Most of these models use rodents, but dogs and pigs have also been successfully introduced (2, 3). However, in these models food allergy is induced using adjuvants and often non-physiological routes of sensitization. Different breeds of animals, types, dosages and formulations of antigen or administration protocols impede direct comparison. The species-specific immunological mechanisms result in phenotypes different from real-life patients. Therefore, well-standardized food allergy animal models have to be defined.

We suggest that companion animals, suffering from adverse food reactions (AFR), may serve as well-suited disease cohorts for comparison, as they i) spontaneously develop allergies independent of artificial cofactors, ii) share the environment, and iii) often even eat similar food as their owners. The present review focuses on immunologically mediated AFR in human and veterinary patients, and particularly elaborates the knowledge gaps.

Epidemiology

Prevalence, age of onset and genetic predisposition

Prevalence of human food allergy is mainly deduced from self-reports, which show that in the USA 6.53% of children and 9.72% of adults are affected (overall: 8.96%), presumably also including intolerances (4). The prevalence for adults drops to 3.49% when specifically asked for allergic reactions to peanuts, tree nuts, fish, and shellfish. In a European study, the number of people with food allergy confirmed by DBPCFC was even lower (0–2.2%) (5). In the USA, self-reported food allergy increased from 9.1% (2001) to 13% (2010), and physician-diagnosed from 5.3% (2001) to 6.5% (2010) (6) due to unclear reasons. In contrast, the numbers for food-specific IgE-sensitizations did not change between 1988-1994 (24.3%) and 2005-2006 (21.6%) in 6-19 year old participants, and even decreased for shrimp (11.2% to 6.1%) (7).

The true prevalence of food allergy in dogs, cats and horses is unknown. In dogs with clinical signs suggestive of allergic dermatitis, the prevalence of AFR (including immunological and non-immunological conditions) was reported to range between 7.6% and 25% (8-11), and AFR was diagnosed in 1.69% of the total canine population presented to a veterinary teaching hospital over 12 months (10). The prevalence of AFR in cats ranged from 0.22% to 6% of animals with cutaneous and from 17% to 22% with gastrointestinal tract signs (12). In horses, there is only anecdotal evidence with few cases documented in peer-reviewed literature (13, 14). Possibly, the condition is under-diagnosed or corrected by owners prior to seeking veterinary attention (15).

In humans, prevalence of food allergy is generally higher in infants (among those younger than 1 year, up to 10% reacted to one of the common food allergens) (16) than in adults and elderly (17). A genetic predisposition for allergy is particularly relevant for children with atopic dermatitis (AD), who frequently suffer from co-existing food allergy (26.13%-35%) (18, 19) (Fig. 1). Differences in allergy prevalence are also found depending on geographic site (Spain/Germany/Australia: 4.6%/16%/19 %) (20), and urban vs. rural environments (21). In dogs, a strong predilection for young (<1 year) or older dogs (>6 years) was described (8-10). Labrador retrievers, West Highland White

terriers, Boxers, Rhodesian ridgebacks and Pug breeds are predisposed to developing AFR. In cats, there seems to be an onset of AFR with ranges from 3 months-11 years (mean age: 4-5 years) (22). The risk for AFR in cats was 13% when suffering from feline atopic dermatitis (23). Siamese or Siamese-cross breeds seem to be at increased risk of developing AFR (24).

Pathogenesis of food allergy

Mechanisms

The best-defined form of food allergy in humans is the IgE-mediated immediate type (25). Encountering a food allergen leads to a Th2-immune reaction (IL-4, IL-13, IL-5), which induce B-cell activation, class-switching to generation of IgE-antibodies against food proteins, and eosinophilic inflammation (26). IgE binds to effector cells such as mast cells (mucosal tissue) and basophils (blood) via high-affinity IgE-receptors. During a subsequent encounter with the food protein, crosslinking of IgE on the surface of those cells induces degranulation and release of mediator substances, responsible for the allergic symptoms. However, besides this immediate type IgE-mediated food allergy, in humans there are syndromes mediated by T cells, immunoglobulins other than IgE, or as of yet unknown mechanisms, such as dietary protein enterocolitis syndrome (27), dietary protein proctitis, dietary protein enteropathy and coeliac disease, *Dermatitis herpetiformis*, food-induced pulmonary haemosiderosis (Heiner's Syndrome) (28), and potentially eosinophilic esophagitis (29).

Mechanisms of AFRs in companion animals are largely unknown. In some canine models, an allergen-specific IgE response can be measured during sensitization and after oral challenge, suggesting that IgE might play a role in the pathogenesis of the disease (30-33). In client-owned dogs with AFR, the duodenal gene expression of Th1, Th2 and Treg-related cytokines was similar to that of normal dogs and did not change with dietary provocation, suggesting that the intestinal mucosa is not the primary site of T-cell activation that finally leads to cutaneous food hypersensitivity (34). The predominant CD8⁺ T-cell phenotype and gene expression in lesional skin of client-owned dogs with AFR persisted after using a novel protein home-cooked diet (ostrich, turkey, horse or goat meat) for at least 8 weeks, whilst clinical signs resolved (35). In a cat colony, 8 cats with vomiting, dermatitis and significant eosinophilia underwent a limited-allergen diet (12 weeks), after which eosinophilia and clinical signs were reduced (36). Histologically, gastric and duodenal specimens revealed a moderate infiltration of eosinophils into the duodenum in only two cats; another two cats had a mild eosinophilic infiltrate in the stomach. In the horse, the mechanism of food allergy is unknown.

Risk factors

Factors influencing oral tolerance are the integrity of the intestinal epithelial barrier, tolerance-inducing antigen-presenting cells (APC) and T-regulatory cells (25). The known risk factors for atopic dermatitis are the same in humans and in companion animals, and are also associated with a higher risk for food allergy (37, 38).

Clinical signs

In human patients, type I food allergy typically manifest as follows: i) gastrointestinal signs (itching and swelling of lips, tongue and throat, gastric problems, diarrhea, intestinal cramps), ii) cutaneous itching, exacerbation of eczema, angioedema or urticaria (Fig. 1), iii) problems with the eyes (conjunctivitis), iv) respiratory distress (rhinitis, asthma), or v) systemically (decreased blood pressure, tachycardia, life-threatening cardiovascular collapse in anaphylactic shock). Symptoms typically occur within minutes to 2-4 hours after ingestion. In a recent study among Portuguese adults (39), who mainly reacted to seafood, various fresh fruits and fish, the most frequently reported symptoms were acute urticaria (AU) and/or angioedema (AE) (48.3 % of the cases), oral allergy syndrome (OAS) (16.6 %), respiratory (15 %) and gastrointestinal symptoms (dyspepsia, abdominal pain, diarrhea and/or vomiting) (6.6 %). The main self-reported symptoms with seafood allergies were AU/AE and respiratory problems. A comparable number of patients (around 7%) reported onset of symptoms either immediately (< 30 min. after ingestion) or delayed (2-24 hours after ingestion). However, when testing patients, IgE-mediated reactions appeared within 30 minutes, while delayed reactions were associated with non-IgE-mediated responses.

Companion animals may spontaneously develop skin (dogs, cats, horses), respiratory (cats, horses) and gastrointestinal reactions due to allergies (dogs, cats), like human patients (40, 41). However, there is no clear evidence of an association between AFR and respiratory symptoms in companion animals, where AFR generally manifests as cutaneous or gastrointestinal abnormalities. In dogs, cutaneous symptoms are commonly reported (Fig. 1) and are frequently indistinguishable from those of atopic dermatitis due to environmental allergens (42, 43). Generalized or localized non-seasonal pruritus (face, ears, paws, axillae, inguinal and perineal regions) is the most frequently described dermatological sign (8-10, 30, 43-45). Otitis externa and recurrent pyoderma with or without pruritus have also been associated with AFR in canines (9, 30, 44). Clinical signs reportedly develop between 4 hours and 14 days after eating the offending food (10, 45) and suggest that more than one pathophysiological mechanism is present. Gastrointestinal signs may include vomiting,

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diarrhoea, weight loss and abdominal discomfort (9, 30, 44, 45). In a prospective study, food was reported as the trigger of urticaria in five dogs, three of them also exhibiting vomiting and diarrhea. Offending foods were potatoes, rice and beef in dogs with only urticaria, and cheese, walnuts and nuts in dogs with both urticaria and gastrointestinal signs. However, in this study the causal relationship with food was established using a non-validated scale (46). Another dog developed urticaria after ingesting peanuts (47). Food allergy was also implicated in three dogs with urticarial vasculitis, and in two of them a relapse of clinical signs was seen after oral beef-challenge (48, 49). Oral allergy syndrome has been reported in one dog. Clinical signs included salivation, lip swelling, quivering of tongue, flushing and pruritus of the abdomen and ears 15 to 30 minutes after provocation with tomato (50).

Between 10 and 30% of cats with AFR show cutaneous (Fig. 1) and gastrointestinal symptoms (22, 51). Earlier reports indicated pruritus at the head and neck in 30-65% of cases (22, 52, 53). However, although more often involved in dietary-related than other allergic diseases, this criterion was not of significant value for the clinical setting (12). Cats with AFR may also present with symmetrical self-induced alopecia, miliary dermatitis, chronic vomiting and diarrhea (12, 54, 55), eosinophilic granulomas, plaques and indolent ulcers (56).

There is very little data about AFR in horses. Anecdotal reports describe pruritus and urticaria (Fig. 1) as possible clinical signs of food allergy. Gastrointestinal symptoms may also be present (13, 15). Sensitization and food-specific IgE in serum are not necessarily clinically relevant (57).

Allergen sources and molecules

The most common foods evoking AFR in Americans are milk, eggs, peanuts, tree nuts, soy, wheat, fish and shellfish, whereas Europeans are also affected by reactions to sesame, lupine, mustard and celery (4, 58). Some of these food allergies (peanut (59), tree nuts, fish, shellfish) persist over the patient's lifetime, whereas others (soy, wheat, egg, milk) are often outgrown (60).

The most common food allergen sources for dogs are beef (34%), chicken (17%), milk and dairy products (15%), lamb (15%) and wheat (14%) (61). For cats, important food sources evoking AFR are beef, chicken and fish (31, 61). Foods associated with AFR in horses anecdotally include potatoes, malt, beet pulp, buckwheat, fish meal, wheat, alfalfa, red and white clover, St. John's wort, chicory, barley and oats (62). Food allergen sources with known allergenic molecules relevant for human and veterinary patients are listed in table 1.

Peanut

In humans, Ara h 1, Ara h 2 and Ara h 3 have been confirmed as markers for peanut sensitization (63), and Ara h 2 and -6 as predictors for severe clinical reactions (64). In contrast, IgE to Ara h 8, -9, and crossreactive carbohydrate determinants (CCDs) have been associated with tolerance to peanuts (65, 66). A single client-owned dog showed urticaria after ingestion of peanuts, however, investigation of the causative protein was not pursued (47). Peanut is not a common food ingested by dogs.

Soy

In humans, Gly m 4, -5, and -6 are considered predictors of severe hyperreactivity (67). Epitopes of the β -subunit of the soybean seed storage protein β -conglycinin (anaphylactogenic allergen in humans) (68), were shown to be antigenic (but not allergenic) in pigs, dogs, rabbits and fish (69), indicating possible cross-species reactivity. Soy is present in many pet foods and a known food allergen in the dog (70). Positive skin tests to soybean meal were seen in equines (71), proposing a possible role of soy in chronic obstructive pulmonary disease. In pigs, transient food allergy to soy may occur after weaning, but can be prevented by soy in the maternal diet before this time point (72).

Tree nuts: hazelnut & walnut

In humans, IgE to the PR-10 molecule Cor a 1 dominated in Northern Europe (73), whereas sensitization to nsLTP Cor a 8 and to 2S-albumin Cor a 14 was observed in the Eastern Mediterranean (74). Among hazelnut allergens, Cor a 14 and the 7S globulin Cor a 9 were suggested as predictors of severe reactions (75). In walnuts, Jug r 3, another nsLTP, indicated an increased risk for systemic reactions (76).

For pets, few reports of nut allergy exist. Walnut was detected as a possible trigger for urticaria in dogs (46), and one individual dog with suspected walnut-induced anaphylaxis had positive prick and intradermal tests to hazelnut and walnut, with Western Blot analysis identifying a 22 kDa protein as IgE target (77). For tree nut allergy, a dog model has been developed based on subcutaneous alum-precipitated allergen injections (78).

Wheat

The major human-relevant allergens in wheat are α -, β -, γ -, ω -gliadins, and low molecular weight (LMW) glutenin (79). The LTP Tri a 14 and the dimeric alpha-amylase inhibitor (AAI) 0.19 (Tri a 28) are predictive for clinical reactivity (80), whereas Tri a 27 (thiol reductase) and Tri a 28 have the highest diagnostic value in occupational settings such as baker's allergy (81). Wheat was among the most frequent elicitors of cutaneous AFR, particularly in dogs (3, 61). Assessing sensitization based on positive skin tests, 15% of canine patients were hyperreactive to wheat (82).

Bet v 1 and crossreactive molecules from Rosaceae fruits

PR-10 molecules are paradigmatic as strong respiratory sensitizers with IgE-crossreactivity to other PR-10 allergens in food. In Northern Europe, the major birch pollen allergen Bet v 1 crossreacts with Pru p 1 in peaches, whereas the stable nsLTP Pru p 3 is a sensitizer and elicitor of allergies in the South (83). Sensitization to recombinant Bet v 1 in an atopic dog model occurred, but did not lead to clinically apparent allergy (84). Naturally, 10-35% of pollen allergic dogs react to birch (reviewed in (40)). For instance, among 1000 canine atopic dermatitis patients in southeast Australia, around 10% showed positive IDT to birch pollen mix (82). However, sensitization explicitly to the Bet v 1-molecule was not investigated. Besides respiratory allergy, crossreactive food most often only causes oral allergy syndrome (OAS), as most PR-10 molecules are digestion-labile. This syndrome was reported in one dog in which sensitisation to Japanese cedar (*Cryptomeria japonica*) led to clinical crossreactivity to fresh tomato (50).

Milk

In human milk allergy, high IgE levels to Bos d 4 (α -lactalbumin), Bos d 5 (β -lactoglobulin) and Bos d 8 (casein) are clinically predictive for a lower success rate of oral allergen immunotherapy to milk (85). Most animal studies refer to allergens present in milk as well as in meat. Meat has a stronger implication in adult pets' diet. Canine IgE-reactivities have been found to beef, pork, lamb and cows' milk, IgG antibodies to beef, pork, lamb, cows' milk, chicken and turkey (86), with unclear clinical relevance. In dogs with AFR, responding to elimination diet, IgE against bovine milk compounds between 51 and 58 kDa (phosphoglucosyltransferase and IgG heavy-chain Bos d 7), and in some patients to unidentified 27, 31, 33, 37 and 42 kDa compounds (87) were found. Bovine serum albumin was identified as possible allergen for beef-allergic canines by immunoblotting and

intradermal testing (88). Furthermore, strong serological crossreactivity of dogs sensitized to beef, lamb and milk was observed, although not correlated with confirmed clinical hypersensitivity (11, 89).

Egg

In human egg allergy, IgE-reactivities change during childhood from Gal d 2 (ovalbumin) to Gal d 1 (ovomucoid) to Gal d 3 (ovotransferrin) (90). Gal d 1 is an established diagnostic marker in humans (91). In pigs, IgE-mediated allergy and anaphylaxis can be induced experimentally with egg proteins (72), and most often Gal d 1 was used as antigen (92, 93). In dogs, no significant differences were found between normal and atopic dogs for anti-egg-IgG. However, dogs with skin disease had significantly more IgE-antibodies to egg and many other antigens than normal dogs (94). In dogs allergic to egg, ovomucoid and ovalbumin are major allergens (95).

Meat

IgE-mediated meat allergy in humans may present as both immediate or delayed-type reactions. Non-protein allergens like galactose- α -1,3-galactose (alpha-gal) have recently gained attention. Alpha-gal epitopes have also been found on porcine peptidases, angiotensin-I-converting enzyme (ACE I), and aminopeptidase N (AP-N) (96). In affected humans, tick bites were associated with red meat allergy (97).

In dogs, this antigen is a self-antigen, whether other antigens from tick bites play a role in canine allergies has so far not been investigated. There are documented cutaneous AFR of dogs to beef, dairy products, and chicken (61), the latter obviously conferring cross-sensitization to other poultry meats and feathers (98). Crossreactive meat allergens are phosphoglucomutase and Bos d 7 (87), Bos d 6 and bovine serum albumin in blot and intradermal test (88).

Fish

In human fish allergy, beta-enolase and fructose-bisphosphate aldolase represent important allergens besides crossreactive parvalbumin (99). They play a role in clinical crossreactivity with white meat from chicken (100) and although not further characterized, likely represent the molecular allergens relevant for fish allergy, especially in cats (101).

Shellfish

Molecular crossreactivity of shellfish antigens with cockroach, house dust mites, molluscs or novel-food insect antigens (102) is due to IgE against sarcoplasmic calcium-binding proteins, arginine kinase, hemocyanin, and especially to tropomyosin (103). No direct evidence points to shellfish as important allergen for veterinary patients. However, as canines and other animals are often sensitized to cockroach and house dust mites (104, 105), crossreactivity with shellfish antigens might be also relevant for domestic animals.

Diagnosis

First, a thorough diagnostic work-up is indispensable for human and veterinary patients to distinguish type I allergy from other AFR, and to choose the appropriate food allergen avoidance diet, which is the only cure for food allergy (Fig. 2). A detailed interview is pivotal in human patients. A food diary may be helpful, including documentation of ancillary factors like consumption of alcohol or medications, exercise performed, or diseases with accompanying fever (review (106)). Second, if IgE-mediated food allergy is likely based on the patient's history, a skin prick test or prick-to-prick test with native food is performed. These detect food allergy with high sensitivity, although specificity is rather low at 50%. It should be acknowledged that the risk of false-positive results may result in unjustified dietary restrictions (107). The third cornerstone of diagnosis is food antigen-specific IgE in serum. The newer singleplex or multiplex testing with molecular allergens improves the diagnostic precision in humans, allows a risk evaluation in a component-specific manner (108), and switches the conservative diagnostic concept "from clinic to molecule" to the novel concept "from molecule to clinic" (109).

Importantly, skin test reactivity and serum IgE in humans do not necessarily correlate with severity of clinical reactions. In addition to specific IgE, the only accepted biomarker in humans, diagnosis has to be confirmed clinically in both human and animal patients (40). Allergic children (≤ 5

years) are likely to outgrow their food allergy. Therefore, serum IgE and skin tests should be performed every 12 months, and once they normalize, an open OFC helps to decide whether foods could be reintroduced to improve quality-of-life and provide important nutrients (106).

If diagnosis cannot be confirmed with the previously mentioned measures, there are other options. One possibility is using an elimination diet to further assess AFRs. During an allergen-free dietary period, symptoms should subside over several weeks. Another option, considered the gold standard in food allergy diagnosis for humans, is the double-blind placebo-controlled provocation test (107). However, this procedure is associated with a risk of systemic reactions, and is time-, cost- and labour-intensive and thus rarely done. Finally, late-phase type IV reactions during food allergy can be verified by atopy patch testing (APT). To guarantee sensitivity, specificity and reproducibility, only the standardized APT technique developed by the European Task Force on Atopic Dermatitis should be used. Due to limited availability, high costs of standardized test substances, and restricted reimbursement, APT is not used routinely for AFR testing (110).

In dogs and cats with suspected AFR, IDT reactivity to food antigens and food-specific IgE are not reliable and therefore not recommended. Repeatability, sensitivity and specificity of food-specific IgE have been unsatisfactory (111-113). Low performance may relate to the test methodology, allergens employed, lack of IgE involvement in canine AFR, or heterogeneity of the study population (113, 114). In dogs, patch testing with food antigens has a high negative predictive value (99.3%) (112) and may be helpful for the choice of an elimination diet. Antigen-specific lymphocyte proliferation was increased in dogs with AFR, AD and atopic-like dermatitis (115), which declined after >6 weeks on elimination diet. This supports a role of these immune cells in the pathogenesis of canine AFR (116). The mast cell activation marker tryptase was determined in skin biopsies of dogs with AD (117, 118) and of cats (119), but is not used as a serum marker for anaphylactic reactions as it is in humans.

Consequently, AFR in cats and dogs are diagnosed by feeding an elimination diet with a novel protein +/- carbohydrate source for ≤ 8 weeks (120). In improved situations, re-challenge with the original diet should lead to clinical deterioration. Patients should subsequently improve again during elimination diet (112), with gastrointestinal signs often subsiding before concurrent dermatological problems. Owners can feed a homemade diet, a commercial diet with hydrolyzed protein, or a commercial diet with proteins unusual for the affected dog. Commercial diets can contain larger protein molecules capable of inducing clinical deterioration in some animals (121, 122) or protein sources not declared on the label (123, 124). However, they remain a practical, workable option (125, 126). A home-cooked diet is thus regarded as the most reliable diagnostic

option. During the elimination diet, the pet must not receive any other food, treats, medications, vitamins or supplements with any protein other than the one chosen for the diet.

Food-specific IgE has been found in horses with allergic skin disease (127), and positive IDT reactions to food occur in allergic horses (128, 129). However, both IDT and serum IgE frequently give false positive reactions in clinically healthy horses (57, 127) and do not correlate well with symptoms (128). Thus, a definitive diagnosis of food allergy in horses can only be confirmed by elimination trial (130).

Prophylaxis, management, and therapy of food allergy

Prophylaxis

According to the hygiene hypothesis, modern environment and life-style (review (131)) decrease contact with pathogens and increase allergy risk, including food allergy. People living on a farm with traditional animal husbandry (132) and consuming raw milk develop asthma less frequently (133). Although there is only limited supporting data in veterinary allergology, similar mechanisms seem to be relevant. Dogs in rural areas develop atopic dermatitis less frequently than those in urban areas, and the same goes for dogs kept mostly outdoors compared to dogs kept in an apartment (134).

The time window for food introduction into the diet of children seems to play a critical role for allergy prevention, as early introduction (≤ 6 months) -including allergenic foods- supports tolerance induction (135). In canines, a small study suggested that feeding homemade food during pregnancy protects against atopic dermatitis (136). In humans, the gut microbiome together with ingested food influences the intestinal immune response (137-139). Probiotics prescribed to pregnant women reduced atopic dermatitis in children during first 2 years of life, but had no effect on food allergy, asthma or atopic sensitization (140). There is currently active research into the canine cutaneous and gastrointestinal microbiome and its relationship with inflammatory and allergic disease (141, 142).

Management

Once food allergy is established, strict avoidance of the allergen is the gold standard in humans. A dietician's advice may help to avoid unnecessary diets and nutritional deficiency, especially in children. For babies with food allergy or at high allergy-risk, who are not breastfed, hydrolyzed formula food should be given for the first 4 months (143, 144). To facilitate allergen

avoidance, current European law requires (potential) content of the 14 most important food allergens to be listed in pre-packed food (145), and information has to be provided in restaurants and for non-prepackaged food. In case avoidance fails and a life-threatening situation occurs, treatment is possible with epinephrine self-injection, prescribed by a physician.

In animals, anaphylactic episodes are rarely observed. Management of AFR in dogs, cats and horses currently also relies on avoidance of the offending food. Either a home-cooked diet, a commercial veterinary prescription diet, or a novel protein over-the-counter (OTC) diet can be selected for the long-term management of AFR in dogs and cats (122, 146). The latter two offer the advantage of enhanced owner compliance compared to home-cooked diets (147). In addition, particularly in young, large breed, rapidly growing dogs, home-cooked diets can be unbalanced and inadequate (148). However, one reason for failure to respond to a commercial novel protein diet is contamination with food ingredients not declared on the label (123, 149), other flavored medications, treats, or supplements may contain soy, pork, and beef (150). Finally, taxonomic relationship between meat sources should be considered to avoid the risk of crossreactivity (89). Formulas available for hypersensitive dogs (120, 126) should be extensively hydrolyzed to avoid recurrence of clinical signs, especially if the proteins were previously fed (126).

Treatment trials

Subcutaneous immunotherapy (SCIT) for food allergens bears a significant risk of serious adverse events in human patients (151), however, it is routine treatment for environmental (pollen, dust mite, animal dander) and insect venom (bee, wasp) allergens (152). Recent studies therefore focus on different routes of administration (review (106)). In oral allergen immunotherapy (OIT), the offending food allergen is ingested with a carrier food. OIT is performed in three steps, i) small amounts of allergen in increasing dosage are administered over a single day under supervision, ii) increasing dosage of allergen every two weeks, and iii) maintenance phase with target dose of allergen ingested daily at home for months or years. OIT is currently being evaluated for peanut, egg and milk allergy, and even trials treating multi-food allergies are ongoing (153). Combination therapies with anti-IgE-antibody omalizumab have proven successful in a first peanut OIT trial (154) by reducing adverse effects and increasing the tolerated allergen dose.

During sublingual immunotherapy (SLIT), allergen extracts in aqueous solutions or as lyo-tablets are solubilized under the tongue for at least 2 minutes. Lower allergen doses are administered and therefore this treatment may be safer than OIT. SLIT has previously been trialed

for peanut allergy; however, most patients discontinued the therapy by the end of year 3. At that time, only 4 of 37 SLIT-treated subjects (10.8%) were fully desensitized to 10 g of peanut powder (155).

For epicutaneous immunotherapy (EPIT), allergens in a round disk chamber are applied onto the healthy skin of patients. This reduces the risk of unwanted systemic reactions. In a clinical trial of children allergic to milk, EPIT for 30 days increased the maximally tolerated amount of milk from 1.77 ml to 23.61 ml. The main adverse effects were mild cutaneous reactions (156). Mechanistically, T-regulatory cells may be attracted to the patch site (157, 158).

There is minimal data on allergen-specific food immunotherapy of AFR for dogs, and none for cats or horses. Immunotherapy utilizing *Listeria monocytogenes* as adjuvant was tested in an atopic canine model (159), where dogs were experimentally sensitized to peanut and other allergens. A single subcutaneous treatment diminished or abolished allergic symptoms (vomiting, diarrhea) after oral challenge and was associated with reduced Ara h 1-specific-IgE in serum of peanut-sensitive dogs.

The safety and efficacy of food allergen-specific sublingual immunotherapy was recently investigated in a small group of client-owned dogs with AFR (160). Food allergen extracts (crude defatted pork meat, chicken meat, beef, fish, cow's milk, crude defatted rice, wheat and corn) were administered for 6 months to dogs (n=7) based on the results of restriction-provocation trials. Sporadic and self-limiting adverse effects of the immunotherapy were reported (vomiting, erythema, pruritus). A reduction $\geq 50\%$ of baseline Canine Atopic Dermatitis Extent and Severity Index (CADESI-04) (161) and 35% reduction of pruritus were observed in treated dogs.

Novel delivery routes of immunotherapy for food allergy, including epicutaneous desensitization (162), are reaching clinics for human patients (163), and are discussed as future concepts in veterinary medicine (164). Intralymphatic allergy vaccines were proposed for the treatment of canine atopic dermatitis (164, 165) and insect bite hypersensitivity in horses (166), but not for food allergy so far. Larger clinical trials are needed before considering allergen-specific immunotherapy as safe and effective treatment to manage dogs with AFR.

Synopsis

Systematic comparison of food allergies in human and veterinary patients provides insights into the influence of genetics, allergen exposure and the shared environment on development of food allergy. This may lead to improved recommendations for prevention and treatment of food allergy. However, currently there are numerous gaps in the knowledge:

- The true prevalence of food allergy in humans is only known for sporadic allergens and from restricted studies, and is not known in dogs, cats and horses. A global map needs to be established allowing prevalence determinations over time.
- The reasons for the increase in self-reported and physician-diagnosed food adverse reaction are not well understood and need to be objectified.
- A definite diagnosis relies on risky provocation tests; a reliable biomarker for food allergy is lacking and would be tremendously useful.
- Although several foods have been accepted as allergen sources for animals, little is known about the causative allergenic molecules. Molecular allergen diagnosis in humans has been helpful in selected patients and could also improve diagnosis and treatment in animals.
- Changes in the immunogenic potency of food by processing should be understood and applicable in daily veterinary practice, similar with what is known in humans.
- There are several novel treatment options underway. However, more studies are needed to understand the mechanisms and to develop practical and relevant biomarkers to evaluate safety and efficacy.

Author contributions

IPS authored the sections on humans and coordinated the writing;

EJJ authored the molecular allergy diagnosis section and helped in the overall manuscript writing;

MDL designed the outline of the systematic review;

MDL and HJ concentrated on the veterinary sections of epidemiology, clinical signs, pathogenesis and treatment;

RSM authored the section describing the diagnosis of adverse food reactions in animals;

JJ concentrated on the epidemiology, symptoms and diagnosis of food allergy in horses.

All authors critically revised and edited the manuscript and approved the final version.

Conflicts of interest

The authors declare no conflict of interest.

Table 1: Summary of most important allergenic molecules from food relevant for humans, and documentation of their relevance for veterinary patients.

Food source	Molecule name(s) or molecular weight (kDa)	Human relevance	Ref	Veterinary relevance	Ref
Peanut				Dog (experimental model)	(47, 167)
				Pig (experimental model)	(72)
	Ara h 1	+	(63)		
	Ara h 2	severe reactions	(63, 64)		
	Ara h 3	+	(63)		
	Ara h 6	severe reactions	(64)		
	Ara h 8	tolerance	(65, 66)		
	Ara h 9	tolerance	(65, 66)		
Soy				Dog	(70)
				Dog (experimental model)	(125)
				Horse (mill dust for pulmonary disease)	(71)
	Gly m 4	severe hyperreactivity	(67)		
	Gly m 5	severe	(67)		
	Gly m 6		(67)		

	75/50 kDa			+	(168)
	31/20 kDa			+	(168)
	β -Conglycinin	anaphylactogenic	(68)	Antigenic in pigs, dogs, rabbits and fish	(69)
Tree nuts					
Hazelnut	Cor a 1	dominant in Northern Europe	(74)		
	Cor a 8	dominant in Athens	(74)		
	Cor a 9	severe reactions	(75)		
	Cor a 14	Eastern Mediterranean; severe reactions	(74, 75)		
Walnut				Dog Dog (experimental model)	(46) (78)
	Jug r 3	risk for systemic reactions	(76)		
Wheat	ω -Gliadins	+	(79)		
	ω -Gliadins	+	(79)		
	ω -Gliadins	+	(79)		
	ω -Gliadins	+	(79)		
	LMW Glutenin	+	(79)		
	Tri a 14	predicts clinical reactivity	(80)		
	Tri a 27	diagnosis of occupational allergy	(81)		
	Tri a 28	predicts clinical reactivity, diagnosis of occupational allergy	(80, 81)		
PR-10 family					
Birch pollen				Dog	(40)

	Bet v 1	responsible for crossreactions to other PR-10 food allergens	(169)	Sensitization in atopic dogs without clinical reactions	(84)
Peach	Pru p 1	Northern Europe	(83)		
	Pru p 3	Southern Europe	(83)		
Milk	Bos d 4	clinically predictive for low success in OIT	(85)		
	Bos d 5	clinically predictive for low success in OIT	(85)		
	Bos d 6			Beef-allergic canines	(88)
	Bos d 7			+ Dogs	(87)
	Bos d 8	clinically predictive for low success in OIT	(85)		
	Phospho-glucomutase			+ Dogs	(87)
	27, 31 33, 37 and 42 kDa			+ Dogs	(87)
	Bovine serum albumin				(88)
Egg	Gal d 1	diagnostic marker	(90)	Dog Pig (experimental model)	(95) (72, 92, 93)
	Gal d 2	+	(90)	Dog	(95)
	Gal d 3	+	(90)		
Meat	Alpha-gal	+	(96)		
	Porcine peptidases	+	(96)		
	Angiotensin-I-converting enzyme (ACE I)	+	(96)		
	Aminopeptidase N (AP-N)	+	(96)		
	Bovine serum albumin			Beef-allergic dogs	(88)
Fish	Parvalbumin	+	(99, 100)		

		crossreactive with chicken meat			
	Enolase	+ crossreactive with chicken meat	(99, 100)		
	Fructose-bisphosphate aldolase	+ crossreactive with chicken meat	(99, 100)		
Shellfish	Sarcoplasmic calcium-binding proteins	+	(103)		
	Arginine kinase	+	(103)		
	Hemocyanin	+	(103)		
	Tropomyosin	+	(103)		

+..... IgE-reactivity/-binding shown

References

1. Bogh KL, van Bilsen J, Glogowski R, Lopez-Exposito I, Bouchaud G, Blanchard C et al. Current challenges facing the assessment of the allergenic capacity of food allergens in animal models. *Clin Transl Allergy* 2016;**6**:21.
2. Buchanan BB and Frick OL. The dog as a model for food allergy. *Ann N Y Acad Sci* 2002;**964**:173-183.
3. Frick OL. Food allergy in atopic dogs. *Adv Exp Med Biol* 1996;**409**:1-7.
4. McGowan EC and Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010. *J Allergy Clin Immunol* 2013;**132**:1216-1219 e1215.
5. Grabenhenrich LB. [The epidemiology of food allergy in Europe]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2016;**59**:745-754.

- Accepted Article
6. Verrill L, Bruns R and Luccioli S. Prevalence of self-reported food allergy in U.S. adults: 2001, 2006, and 2010. *Allergy Asthma Proc* 2015;**36**:458-467.
 7. McGowan EC, Peng RD, Salo PM, Zeldin DC and Keet CA. Changes in Food-Specific IgE Over Time in the National Health and Nutrition Examination Survey (NHANES). *J Allergy Clin Immunol Pract* 2016;**4**:713-720.
 8. Picco F, Zini E, Nett C, Naegeli C, Bigler B, Rufenacht S et al. A prospective study on canine atopic dermatitis and food-induced allergic dermatitis in Switzerland. *Vet Dermatol* 2008;**19**:150-155.
 9. Chesney CJ. Food sensitivity in the dog: a quantitative study. *J Small Anim Pract* 2002;**43**:203-207.
 10. Proverbio D, Perego R, Spada E and Ferro E. Prevalence of adverse food reactions in 130 dogs in Italy with dermatological signs: a retrospective study. *J Small Anim Pract* 2010;**51**:370-374.
 11. Bexley J, Nuttall TJ, Hammerberg B and Halliwell RE. Co-sensitization and cross-reactivity between related and unrelated food allergens in dogs - a serological study. *Vet Dermatol* 2016;
 12. Hobi S, Linek M, Marignac G, Olivry T, Beco L, Nett C et al. Clinical characteristics and causes of pruritus in cats: a multicentre study on feline hypersensitivity-associated dermatoses. *Vet Dermatol* 2011;**22**:406-413.
 13. Miyazawa K, Ito M and Ohsaki K. An equine case of urticaria associated with dry garlic feeding. *J Vet Med Sci* 1991;**53**:747-748.
 14. Volland-Francqueville M and Sabbah A. [Recurrent or chronic urticaria in thoroughbred race-horses: clinical observations]. *Eur Ann Allergy Clin Immunol* 2004;**36**:9-12.
 15. Littlewood JD. Food allergy in the horse. *Journal of equine veterinary science* 2002;**22**:129.
 16. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011;**127**:668-676 e661-662.
 17. Jensen-Jarolim E and Jensen SA. Food allergies in the elderly: Collecting the evidence. *Ann Allergy Asthma Immunol* 2016;**117**:472-475.

- Accepted Article
18. Mavroudi A, Karagiannidou A, Xinias I, Cassimos D, Karantaglis N, Farmaki E et al. Assessment of IgE-mediated food allergies in children with atopic dermatitis. *Allergol Immunopathol (Madr)* 2016;
 19. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA and Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;**101**:E8.
 20. Woods RK, Abramson M, Bailey M and Walters EH. International prevalences of reported food allergies and intolerances. Comparisons arising from the European Community Respiratory Health Survey (ECRHS) 1991-1994. *Eur J Clin Nutr* 2001;**55**:298-304.
 21. Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Bohm O and von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000;**30**:187-193.
 22. Bryan J and Frank LA. Food allergy in the cat: a diagnosis by elimination. *J Feline Med Surg* 2010;**12**:861-866.
 23. Ravens PA, Xu BJ and Vogelnest LJ. Feline atopic dermatitis: a retrospective study of 45 cases (2001-2012). *Vet Dermatol* 2014;**25**:95-102, e127-108.
 24. Roudebush P, Guilford WG and H.A. J: Adverse reaction to food. In Small animal clinical nutrition. Edited by M. S. Hand, C. D. Thatcher, R. L. Remillard, P. Roudebush and B. J. Novotny: Mark Morris Institute; 2010.
 25. Iweala OI and Burks AW. Food Allergy: Our Evolving Understanding of Its Pathogenesis, Prevention, and Treatment. *Curr Allergy Asthma Rep* 2016;**16**:37.
 26. Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ and Nadeau KC. Molecular and cellular mechanisms of food allergy and food tolerance. *J Allergy Clin Immunol* 2016;**137**:984-997.
 27. Weinberger T, Feuille E, Thompson C and Nowak-Wegrzyn A. Chronic food protein-induced enterocolitis syndrome: Characterization of clinical phenotype and literature review. *Ann Allergy Asthma Immunol* 2016;**117**:227-233.
 28. Moissidis I, Chaidaroon D, Vichyanond P and Bahna SL. Milk-induced pulmonary disease in infants (Heiner syndrome). *Pediatr Allergy Immunol* 2005;**16**:545-552.
 29. McGowan EC and Platts-Mills TA. Eosinophilic Esophagitis From an Allergy Perspective: How to Optimally Pursue Allergy Testing & Dietary Modification in the Adult Population. *Curr Gastroenterol Rep* 2016;**18**:58.

- Accepted Article
30. Jackson HA, Jackson MW, Coblentz L and Hammerberg B. Evaluation of the clinical and allergen specific serum immunoglobulin E responses to oral challenge with cornstarch, corn, soy and a soy hydrolysate diet in dogs with spontaneous food allergy. *Vet Dermatol* 2003;**14**:181-187.
 31. Day MJ. The canine model of dietary hypersensitivity. *Proc Nutr Soc* 2005;**64**:458-464.
 32. Kimber I, Dearman RJ, Penninks AH, Knippels LM, Buchanan RB, Hammerberg B et al. Assessment of protein allergenicity on the basis of immune reactivity: animal models. *Environ Health Perspect* 2003;**111**:1125-1130.
 33. Hammerberg B, Jackson HA, Burks W and Paps J. Spontaneous IgE associated food allergy in dogs as a model of human peanut allergy. *Journal of Allergy and Clinical Immunology* 2005;**115**:S34.
 34. Veenhof EZ, Rutten VP, van Noort R, Knol EF and Willemse T. Evaluation of T-cell activation in the duodenum of dogs with cutaneous food hypersensitivity. *Am J Vet Res* 2010;**71**:441-446.
 35. Veenhof EZ, Knol EF, Schlotter YM, Vernooij JC, Rutten VP and Willemse T. Characterisation of T cell phenotypes, cytokines and transcription factors in the skin of dogs with cutaneous adverse food reactions. *Vet J* 2011;**187**:320-324.
 36. Hirt R and Iben C. Possible food allergy in a colony of cats. *J Nutr* 1998;**128**:2792S-2794S.
 37. Jensen-Jarolim E, Herrmann I, Panakova L and Janda J: Allergic and Atopic Eczema in Humans and Their Animals. In *Comparative Medicine: Diseases linking humans with their animals*. . Edited by E. Jensen-Jarolim: Springer International Publishing Switzerland; 2017:131-150.
 38. Jensen-Jarolim E, Pali-Scholl I and Roth-Walter F. Animal studies with significant outcomes for human IgE-mediated allergy II. From atopic barrier and immune modulatory microbiome to allergen immunotherapy. *Current Opinion in Allergy and Clinical Immunology* 2017;in review.
 39. Lozoya-Ibanez C, Morgado-Nunes S, Rodrigues A, Lobo C and Taborda-Barata L. Prevalence and clinical features of adverse food reactions in Portuguese adults. *Allergy Asthma Clin Immunol* 2016;**12**:36.

- Accepted Article
40. Jensen-Jarolim E, Einhorn L, Herrmann I, Thalhammer JG and Panakova L. Pollen Allergies in Humans and their Dogs, Cats and Horses: Differences and Similarities. *Clin Transl Allergy* 2015;**5**:15.
 41. Hufnagl K, Hirt R and Robibaro B: Out of breath: asthma in humans and their animals. In *Comparative Medicine: Diseases linking humans with their animals*. . Edited by E. Jensen-Jarolim: Springer International Publishing Switzerland; 2017:71-85.
 42. Gaschen FP and Merchant SR. Adverse food reactions in dogs and cats. *Vet Clin North Am Small Anim Pract* 2011;**41**:361-379.
 43. Favrot C, Steffan J, Seewald W and Picco F. A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. *Vet Dermatol* 2010;**21**:23-31.
 44. Loeffler A, Lloyd DH, Bond R, Kim JY and Pfeiffer DU. Dietary trials with a commercial chicken hydrolysate diet in 63 pruritic dogs. *Vet Rec* 2004;**154**:519-522.
 45. Jackson HA and Hammerberg B. Evaluation of a spontaneous canine model of immunoglobulin E-mediated food hypersensitivity: dynamic changes in serum and fecal allergen-specific immunoglobulin E values relative to dietary change. *Comp Med* 2002;**52**:316-321.
 46. Rostaher A, Hofer-Inteeworn N, Kummerle-Fraune C, Fischer NM and Favrot C. Triggers, risk factors and clinico-pathological features of urticaria in dogs - a prospective observational study of 24 cases. *Vet Dermatol* 2016;
 47. Kang MH and Park HM. Putative peanut allergy-induced urticaria in a dog. *Can Vet J* 2012;**53**:1203-1206.
 48. Nichols PR, Morris DO and Beale KM. A retrospective study of canine and feline cutaneous vasculitis. *Vet Dermatol* 2001;**12**:255-264.
 49. Declercq J. Urticarial vasculitis in a French bulldog. *Vet Dermatol* 2015;**26**:72-73.
 50. Fujimura M, Ohmori K, Masuda K, Tsujimoto H and Sakaguchi M. Oral allergy syndrome induced by tomato in a dog with Japanese cedar (*Cryptomeria japonica*) pollinosis. *J Vet Med Sci* 2002;**64**:1069-1070.
 51. White SD and Sequoia D. Food hypersensitivity in cats: 14 cases (1982-1987). *J Am Vet Med Assoc* 1989;**194**:692-695.

- Accepted Article
52. Guaguère E. Food intolerance in cats with cutaneous manifestations: a review of 17 cases. *Veterinary Allergy and Clinical Immunology* 1996;**4**:90-98.
 53. Rosser EJ: Food allergy in the cat: a prospective study of 13 cats. In *Advances in Veterinary Dermatology*. Edited by P. J. Ihrke, I. Mason and S. D. Shite: Pergamon Press; 1993:33-39. vol 2.]
 54. Guilford WG, Jones BR, Markwell PJ, Arthur DG, Collett MG and Harte JG. Food sensitivity in cats with chronic idiopathic gastrointestinal problems. *J Vet Intern Med* 2001;**15**:7-13.
 55. Guilford WG, Markwell PJ, Jones BR, Harte JG and Wills JM. Prevalence and causes of food sensitivity in cats with chronic pruritus, vomiting or diarrhea. *J Nutr* 1998;**128**:2790S-2791S.
 56. Buckley L and Nuttall T. Feline eosinophilic granuloma complex(ities): some clinical clarification. *J Feline Med Surg* 2012;**14**:471-481.
 57. Dupont S, De Spiegeleer A, Liu DJ, Lefere L, van Doorn DA and Hesta M. A commercially available immunoglobulin E-based test for food allergy gives inconsistent results in healthy ponies. *Equine Vet J* 2016;**48**:109-113.
 58. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;**126**:S1-58.
 59. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W and Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol* 2001;**107**:367-374.
 60. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M et al. ICON: food allergy. *J Allergy Clin Immunol* 2012;**129**:906-920.
 61. Mueller RS, Olivry T and Prelaud P. Critically appraised topic on adverse food reactions of companion animals (2): common food allergen sources in dogs and cats. *BMC Vet Res* 2016;**12**:9.
 62. Rees CA: Disorders of the skin. In *Equine Internal Medicine*. Edited by S. M. Reed, W. M. Bayly and D. C. Sellon: Elsevier; 2009. vol 3rd edition.]
 63. Faber MA, Donne I, Herrebosch E, Sabato V, Hagendorens MM, Bridts CH et al. Sensitization profiles to peanut allergens in Belgium; cracking the code in infants, children and adults. *Acta Clin Belg* 2016;**71**:32-37.

64. Kukkonen AK, Pelkonen AS, Makinen-Kiljunen S, Voutilainen H and Makela MJ. Ara h 2 and Ara 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled study. *Allergy* 2015;**70**:1239-1245.
65. Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M, Seneviratne S, Hanschmann KM, Vogel L et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy* 2015;**70**:391-407.
66. Suratannon N, Ngamphaiboon J, Wongpiyabovorn J, Puripokai P and Chatchatee P. Component-resolved diagnostics for the evaluation of peanut allergy in a low-prevalence area. *Pediatr Allergy Immunol* 2013;**24**:665-670.
67. Berneder M, Bublin M, Hoffmann-Sommergruber K, Hawranek T and Lang R. Allergen chip diagnosis for soy-allergic patients: Gly m 4 as a marker for severe food-allergic reactions to soy. *Int Arch Allergy Immunol* 2013;**161**:229-233.
68. Adachi A, Horikawa T, Shimizu H, Sarayama Y, Ogawa T, Sjolander S et al. Soybean beta-conglycinin as the main allergen in a patient with food-dependent exercise-induced anaphylaxis by tofu: food processing alters pepsin resistance. *Clin Exp Allergy* 2009;**39**:167-173.
69. Taliercio E, Loveless TM, Turano MJ and Kim SW. Identification of epitopes of the beta subunit of soybean beta-conglycinin that are antigenic in pigs, dogs, rabbits and fish. *J Sci Food Agric* 2014;**94**:2289-2294.
70. Jeffers JG, Meyer EK and Sosis EJ. Responses of dogs with food allergies to single-ingredient dietary provocation. *J Am Vet Med Assoc* 1996;**209**:608-611.
71. Halliwell RE, Fleischman JB, Mackay-Smith M, Beech J and Gunson DE. The role of allergy in chronic pulmonary disease of horses. *J Am Vet Med Assoc* 1979;**174**:277-281.
72. Rupa P, Schmied J and Wilkie BN. Porcine allergy and IgE. *Vet Immunol Immunopathol* 2009;**132**:41-45.
73. Blanc F, Bernard H, Ah-Leung S, Przybylski-Nicaise L, Skov PS, Purohit A et al. Further studies on the biological activity of hazelnut allergens. *Clin Transl Allergy* 2015;**5**:26.
74. Buyuktiryaki B, Cavkaytar O, Sahiner UM, Yilmaz EA, Yavuz ST, Soyer O et al. Cor a 14, Hazelnut-Specific IgE, and SPT as a Reliable Tool in Hazelnut Allergy Diagnosis in Eastern Mediterranean Children. *J Allergy Clin Immunol Pract* 2016;**4**:265-272 e263.

75. Brandstrom J, Nopp A, Johansson SG, Lilja G, Sundqvist AC, Borres MP et al. Basophil allergen threshold sensitivity and component-resolved diagnostics improve hazelnut allergy diagnosis. *Clin Exp Allergy* 2015;**45**:1412-1418.
76. Scala E, Till SJ, Asero R, Abeni D, Guerra EC, Pirrotta L et al. Lipid transfer protein sensitization: reactivity profiles and clinical risk assessment in an Italian cohort. *Allergy* 2015;**70**:933-943.
77. Rostaher A, Fischer N, Kuemmerle-Fraune C, Couturier N and Favrot C. Walnut induced anaphylactic reaction in a dog. *Veterinary Dermatology* 2016;**27**:67.
78. Teuber SS, Del Val G, Morigasaki S, Jung HR, Eisele PH, Frick OL et al. The atopic dog as a model of peanut and tree nut food allergy. *J Allergy Clin Immunol* 2002;**110**:921-927.
79. Sotkovsky P, Sklenar J, Halada P, Cinova J, Setinova I, Kainarova A et al. A new approach to the isolation and characterization of wheat flour allergens. *Clin Exp Allergy* 2011;**41**:1031-1043.
80. Makela MJ, Eriksson C, Kotaniemi-Syrjanen A, Palosuo K, Marsh J, Borres M et al. Wheat allergy in children - new tools for diagnostics. *Clin Exp Allergy* 2014;**44**:1420-1430.
81. Sander I, Rihs HP, Doekes G, Quirce S, Krop E, Rozynek P et al. Component-resolved diagnosis of baker's allergy based on specific IgE to recombinant wheat flour proteins. *J Allergy Clin Immunol* 2015;**135**:1529-1537.
82. Mueller RS, Bettenay SV and Tideman L. Aero-allergens in canine atopic dermatitis in southeastern Australia based on 1000 intradermal skin tests. *Aust Vet J* 2000;**78**:392-399.
83. Uasuf CG, Villalta D, Conte ME, Di Sano C, Barrale M, Cantisano V et al. Different co-sensitizations could determine different risk assessment in peach allergy? Evaluation of an anaphylactic biomarker in Pru p 3 positive patients. *Clin Mol Allergy* 2015;**13**:30.
84. Egli KS, Schiessl B, Roosje PJ, Seewald W, Forster U, Peel JE et al. Evaluation of the usefulness of sensitization to aeroallergens as a model for canine atopic dermatitis in genetically predisposed Beagles. *Am J Vet Res* 2002;**63**:1329-1336.
85. Kuitunen M, Englund H, Remes S, Moverare R, Pelkonen A, Borres MP et al. High IgE levels to alpha-lactalbumin, beta-lactoglobulin and casein predict less successful cow's milk oral immunotherapy. *Allergy* 2015;**70**:955-962.

86. Zimmer A, Bexley J, Halliwell RE and Mueller RS. Food allergen-specific serum IgG and IgE before and after elimination diets in allergic dogs. *Vet Immunol Immunopathol* 2011;**144**:442-447.
87. Martin A, Sierra MP, Gonzalez JL and Arevalo MA. Identification of allergens responsible for canine cutaneous adverse food reactions to lamb, beef and cow's milk. *Vet Dermatol* 2004;**15**:349-356.
88. Ohmori K, Masuda K, Kawarai S, Yasuda N, Sakaguchi M and Tsujimoto H. Identification of bovine serum albumin as an IgE-reactive beef component in a dog with food hypersensitivity against beef. *J Vet Med Sci* 2007;**69**:865-867.
89. Bexley J, Nuttall TJ, Hammerberg B and Halliwell RE. Serological cross reactivity between beef, lamb and cows' milk allergen extracts in dogs. *Veterinary Dermatology* 2016;**27**:9.
90. Kim J, Lee J, Park MR, Han Y, Shin M and Ahn K. Special consideration is required for the component-resolved diagnosis of egg allergy in infants. *Ann Allergy Asthma Immunol* 2014;**112**:53-57.
91. Sato S, Yanagida N, Ohtani K, Koike Y and Ebisawa M. A review of biomarkers for predicting clinical reactivity to foods with a focus on specific immunoglobulin E antibodies. *Curr Opin Allergy Clin Immunol* 2015;**15**:250-258.
92. Rupa P, Hamilton K, Cirinna M and Wilkie BN. Porcine IgE in the context of experimental food allergy: purification and isotype-specific antibodies. *Vet Immunol Immunopathol* 2008;**125**:303-314.
93. Schmied J, Rupa P, Garvie S and Wilkie B. Immune response phenotype of allergic versus clinically tolerant pigs in a neonatal swine model of allergy. *Vet Immunol Immunopathol* 2013;**154**:17-24.
94. Foster AP, Knowles TG, Moore AH, Cousins PD, Day MJ and Hall EJ. Serum IgE and IgG responses to food antigens in normal and atopic dogs, and dogs with gastrointestinal disease. *Vet Immunol Immunopathol* 2003;**92**:113-124.
95. Shimakura H, Uchiyama J, Saito T, Miyaji K, Fujimura M, Masuda K et al. IgE reactivity to hen egg white allergens in dogs with cutaneous adverse food reactions. *Vet Immunol Immunopathol* 2016;**177**:52-57.

- Accepted Article
96. Hilger C, Fischer J, Swiontek K, Hentges F, Lehnert C, Eberlein B et al. Two galactose-alpha-1,3-galactose carrying peptidases from pork kidney mediate anaphylactogenic responses in delayed meat allergy. *Allergy* 2016;**71**:711-719.
 97. Commins SP and Platts-Mills TA. Tick bites and red meat allergy. *Curr Opin Allergy Clin Immunol* 2013;**13**:354-359.
 98. Olivry T, Bexley J, Michalak A and Mougeot I. Extensive protein hydrolyzation is indispensable to prevent IgE-mediated food allergen recognition. *Veterinary Dermatology* 2016;**27**:47.
 99. Kuehn A, Hilger C, Lehnert-Weber C, Codreanu-Morel F, Morisset M, Metz-Favre C et al. Identification of enolases and aldolases as important fish allergens in cod, salmon and tuna: component resolved diagnosis using parvalbumin and the new allergens. *Clin Exp Allergy* 2013;**43**:811-822.
 100. Kuehn A, Codreanu-Morel F, Lehnert-Weber C, Doyen V, Gomez-Andre SA, Bienvenu F et al. Cross-reactivity to fish and chicken meat - a new clinical syndrome. *Allergy* 2016;
 101. Vogelnest LJ and Cheng KY. Cutaneous adverse food reactions in cats: retrospective evaluation of 17 cases in a dermatology referral population (2001-2011). *Aust Vet J* 2013;**91**:443-451.
 102. Broekman H, Verhoeckx KC, den Hartog Jager CF, Kruizinga AG, Pronk-Kleinjan M, Remington BC et al. Majority of shrimp-allergic patients are allergic to mealworm. *J Allergy Clin Immunol* 2016;**137**:1261-1263.
 103. Pascal M, Grishina G, Yang AC, Sanchez-Garcia S, Lin J, Towle D et al. Molecular Diagnosis of Shrimp Allergy: Efficiency of Several Allergens to Predict Clinical Reactivity. *J Allergy Clin Immunol Pract* 2015;**3**:521-529 e510.
 104. Chanthick C, Anaman S and Buathet K. The prevalence of positive intradermal allergy tests in 114 dogs with atopic dermatitis in the Bangkok metropolis, Thailand. *Vet Immunol Immunopathol* 2008;**126**:256-262.
 105. Masuda K, Sakaguchi M, Fujiwara S, Kurata K, Yamashita K, Odagiri T et al. Positive reactions to common allergens in 42 atopic dogs in Japan. *Vet Immunol Immunopathol* 2000;**73**:193-204.
 106. Kulis M, Wright BL, Jones SM and Burks AW. Diagnosis, management, and investigational therapies for food allergies. *Gastroenterology* 2015;**148**:1132-1142.

107. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;**134**:1016-1025 e1043.
108. Canonica GW, Ansotegui IJ, Pawankar R, Schmid-Grendelmeier P, van Hage M, Baena-Cagnani CE et al. A WAO - ARIA - GA(2)LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J* 2013;**6**:17.
109. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S et al. EAACI Molecular Allergology User's Guide. *Pediatr Allergy Immunol* 2016;**27 Suppl 23**:1-250.
110. Wollenberg A and Vogel S. Patch testing for noncontact dermatitis: the atopy patch test for food and inhalants. *Curr Allergy Asthma Rep* 2013;**13**:539-544.
111. Wilhelm S and Favrot C. [Food hypersensitivity dermatitis in the dog: diagnostic possibilities]. *Schweiz Arch Tierheilkd* 2005;**147**:165-171.
112. Bethlehem S, Bexley J and Mueller RS. Patch testing and allergen-specific serum IgE and IgG antibodies in the diagnosis of canine adverse food reactions. *Vet Immunol Immunopathol* 2012;**145**:582-589.
113. Mueller RS and Tsohalis J. Evaluation of serum allergen-specific IgE for the diagnosis of food adverse reactions in the dog. *Veterinary Dermatology* 1998;**9**:167-171.
114. Kunkle G and Horner S. Validity of skin testing for diagnosis of food allergy in dogs. *J Am Vet Med Assoc* 1992;**200**:677-680.
115. Suto A, Suto Y, Onohara N, Tomizawa Y, Yamamoto-Sugawara Y, Okayama T et al. Food allergens inducing a lymphocyte-mediated immunological reaction in canine atopic-like dermatitis. *J Vet Med Sci* 2015;**77**:251-254.
116. Ishida R, Masuda K, Kurata K, Ohno K and Tsujimoto H. Lymphocyte blastogenic responses to inciting food allergens in dogs with food hypersensitivity. *J Vet Intern Med* 2004;**18**:25-30.
117. Olivry T, Mayhew D, Paps JS, Linder KE, Peredo C, Rajpal D et al. Early Activation of Th2/Th22 Inflammatory and Pruritogenic Pathways in Acute Canine Atopic Dermatitis Skin Lesions. *J Invest Dermatol* 2016;**136**:1961-1969.
118. von Ruedorffer U, Fisch R, Peel J, Roosje P, Griot-Wenk M and Welle M. Flea bite hypersensitivity: new aspects on the involvement of mast cells. *Vet J* 2003;**165**:149-156.
119. Roosje PJ, Koeman JP, Thepen T and Willemse T. Mast cells and eosinophils in feline allergic dermatitis: a qualitative and quantitative analysis. *J Comp Pathol* 2004;**131**:61-69.

- Accepted Article
120. Olivry T, Mueller RS and Prelaud P. Critically appraised topic on adverse food reactions of companion animals (1): duration of elimination diets. *BMC Vet Res* 2015;**11**:225.
 121. Ricci R, Hammerberg B, Paps J, Contiero B and Jackson H. A comparison of the clinical manifestations of feeding whole and hydrolysed chicken to dogs with hypersensitivity to the native protein. *Veterinary Dermatology* 2010;**21**:358-366.
 122. Olivry T and Bizikova P. A systematic review of the evidence of reduced allergenicity and clinical benefit of food hydrolysates in dogs with cutaneous adverse food reactions. *Vet Dermatol* 2010;**21**:32-41.
 123. Ricci R, Granato A, Vascellari M, Boscarato M, Palagiano C, Andrighetto I et al. Identification of undeclared sources of animal origin in canine dry foods used in dietary elimination trials. *J Anim Physiol Anim Nutr (Berl)* 2013;**97 Suppl 1**:32-38.
 124. Raditic DM, Remillard RL and Tater KC. ELISA testing for common food antigens in four dry dog foods used in dietary elimination trials. *J Anim Physiol Anim Nutr (Berl)* 2011;**95**:90-97.
 125. Puigdemont A, Brazis P, Serra M and Fondati A. Immunologic responses against hydrolyzed soy protein in dogs with experimentally induced soy hypersensitivity. *Am J Vet Res* 2006;**67**:484-488.
 126. Bizikova P and Olivry T. A randomized, double-blinded crossover trial testing the benefit of two hydrolysed poultry-based commercial diets for dogs with spontaneous pruritic chicken allergy. *Vet Dermatol* 2016;**27**:289-e270.
 127. Lorch G, Hillier A, Kwochka KW, Saville WA and LeRoy BE. Results of intradermal tests in horses without atopy and horses with atopic dermatitis or recurrent urticaria. *Am J Vet Res* 2001;**62**:1051-1059.
 128. Lorch G, Hillier A, Kwochka KW, Saville WJ, Kohn CW and LeRoy BE. Comparison of immediate intradermal test reactivity with serum IgE quantitation by use of a radioallergosorbent test and two ELISA in horses with and without atopy. *J Am Vet Med Assoc* 2001;**218**:1314-1322.
 129. Rendle DI, Durham AE, Wylie CE and Newton JR: Results of intradermal testing for the investigation of atopic dermatitis and recurrent urticaria in 50 horses in the south of England. In Equine Veterinary Education. Edited by T. Mair; 2010:616-622. vol Ed 22.]

- Accepted Article
130. Noli C, Foster A and Rosenkrantz W: Diagnostic Workup of Equine Atopic Disease. In Veterinary Allergy. Edited by W. Rosenkrantz and S. D. White; 2013.
 131. Platts-Mills TA. The allergy epidemics: 1870-2010. *J Allergy Clin Immunol* 2015;**136**:3-13.
 132. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE et al. Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. *N Engl J Med* 2016;**375**:411-421.
 133. Debarry J, Garn H, Hanuszkiewicz A, Dickgreber N, Blumer N, von Mutius E et al. *Acinetobacter lwoffii* and *Lactococcus lactis* strains isolated from farm cowsheds possess strong allergy-protective properties. *J Allergy Clin Immunol* 2007;**119**:1514-1521.
 134. Meury S, Molitor V, Doherr MG, Roosje P, Leeb T, Hobi S et al. Role of the environment in the development of canine atopic dermatitis in Labrador and golden retrievers. *Vet Dermatol* 2011;**22**:327-334.
 135. Chan ES, Cummings C, Canadian Paediatric Society CPC and Allergy S. Dietary exposures and allergy prevention in high-risk infants: A joint statement with the Canadian Society of Allergy and Clinical Immunology. *Paediatr Child Health* 2013;**18**:545-554.
 136. Nodtvedt A, Bergvall K, Sallander M, Egenvall A, Emanuelson U and Hedhammar A. A case-control study of risk factors for canine atopic dermatitis among boxer, bullterrier and West Highland white terrier dogs in Sweden. *Vet Dermatol* 2007;**18**:309-315.
 137. Simonyte Sjodin K, Vidman L, Ryden P and West CE. Emerging evidence of the role of gut microbiota in the development of allergic diseases. *Curr Opin Allergy Clin Immunol* 2016;**16**:390-395.
 138. Diesner SC, Bergmayr C, Pfitzner B, Assmann V, Krishnamurthy D, Starkl P et al. A distinct microbiota composition is associated with protection from food allergy in an oral mouse immunization model. *Clin Immunol* 2016;**173**:10-18.
 139. Barcik W, Untersmayr E, Pali-Scholl I, O'Mahony L and Frei R. Influence of microbiome and diet on immune responses in food allergy models. *Drug Discovery Today: Disease Models* 2016;in press.
 140. Dotterud CK, Storro O, Johnsen R and Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol* 2010;**163**:616-623.
 141. Pierezan F, Olivry T, Paps JS, Lawhon SD, Wu J, Steiner JM et al. The skin microbiome in allergen-induced canine atopic dermatitis. *Vet Dermatol* 2016;**27**:332-e382.

- Accepted Article
142. Xu J, Verbrugghe A, Lourenco M, Janssens GP, Liu DJ, Van de Wiele T et al. Does canine inflammatory bowel disease influence gut microbial profile and host metabolism? *BMC Vet Res* 2016;**12**:114.
 143. von Berg A, Filipiak-Pittroff B, Kramer U, Link E, Bollrath C, Brockow I et al. Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). *J Allergy Clin Immunol* 2008;**121**:1442-1447.
 144. Schafer T, Bauer CP, Beyer K, Bufe A, Friedrichs F, Gieler U et al. S3-Guideline on allergy prevention: 2014 update: Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Society for Pediatric and Adolescent Medicine (DGKJ). *Allergo J Int* 2014;**23**:186-199.
 145. European Parliament and Council of the European Union. Regulation on the provision of food information to consumers. Directive 2000/13/EC, 2011. <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=en>.
 146. Loeffler A, Soares-Magalhaes R, Bond R and Lloyd DH. A retrospective analysis of case series using home-prepared and chicken hydrolysate diets in the diagnosis of adverse food reactions in 181 pruritic dogs. *Vet Dermatol* 2006;**17**:273-279.
 147. Johnson LN, Linder DE, Heinze CR, Kehs RL and Freeman LM. Evaluation of owner experiences and adherence to home-cooked diet recipes for dogs. *J Small Anim Pract* 2016;**57**:23-27.
 148. Streiff EL, Zwischenberger B, Butterwick RF, Wagner E, Iben C and Bauer JE. A comparison of the nutritional adequacy of home-prepared and commercial diets for dogs. *J Nutr* 2002;**132**:1698S-1700S.
 149. Willis-Mahn C, Remillard R and Tater K. ELISA testing for soy antigens in dry dog foods used in dietary elimination trials. *J Am Anim Hosp Assoc* 2014;**50**:383-389.
 150. Parr JM and Remillard RL. Common confounders of dietary elimination trials contain the antigens soy, pork, and beef. *J Am Anim Hosp Assoc* 2014;**50**:298-304.
 151. Nelson HS, Lahr J, Rule R, Bock A and Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;**99**:744-751.

152. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014;**69**:854-867.
153. Begin P, Winterroth LC, Dominguez T, Wilson SP, Bacal L, Mehrotra A et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. *Allergy Asthma Clin Immunol* 2014;**10**:1.
154. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M and Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013;**132**:1368-1374.
155. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM et al. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial. *J Allergy Clin Immunol* 2015;**135**:1240-1248 e1241-1243.
156. Dupont C, Kalach N, Soulaïnes P, Legoue-Morillon S, Piloquet H and Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. *J Allergy Clin Immunol* 2010;**125**:1165-1167.
157. Tordesillas L, Mondoulet L, Blazquez AB, Benhamou PH, Sampson HA and Berin MC. Epicutaneous immunotherapy induces gastrointestinal LAP+ regulatory T cells and prevents food-induced anaphylaxis. *J Allergy Clin Immunol* 2016;
158. Jones SM, Agbotounou WK, Fleischer DM, Burks AW, Pesek RD, Harris MW et al. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: A phase 1 study using the Viaskin patch. *J Allergy Clin Immunol* 2016;**137**:1258-1261 e1251-1210.
159. Frick OL, Teuber SS, Buchanan BB, Morigasaki S and Umetsu DT. Allergen immunotherapy with heat-killed *Listeria monocytogenes* alleviates peanut and food-induced anaphylaxis in dogs. *Allergy* 2005;**60**:243-250.
160. Maina E and Cox E. A double blind, randomized, placebo controlled trial of the efficacy, quality of life and safety of food allergen-specific sublingual immunotherapy in client owned dogs with adverse food reactions: a small pilot study. *Vet Dermatol* 2016;**27**:361-e391.
161. Olivry T, Saridomichelakis M, Nuttall T, Bensignor E, Griffin CE, Hill PB et al. Validation of the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4, a simplified severity scale for assessing skin lesions of atopic dermatitis in dogs. *Vet Dermatol* 2014;**25**:77-85, e25.

162. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol* 2016;
163. Senti G and Kundig TM. Novel Delivery Routes for Allergy Immunotherapy: Intralymphatic, Epicutaneous, and Intradermal. *Immunol Allergy Clin North Am* 2016;**36**:25-37.
164. DeBoer DJ. The future of immunotherapy for canine atopic dermatitis: a review. *Vet Dermatol* 2017;**28**:25-e26.
165. Fischer N, Rostaher A and Favrot C. [Intralymphatic immunotherapy: An effective and safe alternative route for canine atopic dermatitis]. *Schweiz Arch Tierheilkd* 2016;**158**:646-652.
166. Jonsdottir S, Svansson V, Stefansdottir SB, Schupbach G, Rhyner C, Marti E et al. A preventive immunization approach against insect bite hypersensitivity: Intralymphatic injection with recombinant allergens in Alum or Alum and monophosphoryl lipid A. *Vet Immunol Immunopathol* 2016;**172**:14-20.
167. Marsella R. Experimental model for peanut allergy by epicutaneous sensitization in atopic beagle dogs. *Exp Dermatol* 2015;**24**:711-712.
168. Serra M, Brazis P, Fondati A and Puigdemont A. Assessment of IgE binding to native and hydrolyzed soy protein in serum obtained from dogs with experimentally induced soy protein hypersensitivity. *Am J Vet Res* 2006;**67**:1895-1900.
169. Kleine-Tebbe J and Herold DA. [Cross-reactive allergen clusters in pollen-associated food allergy]. *Hautarzt* 2003;**54**:130-137.

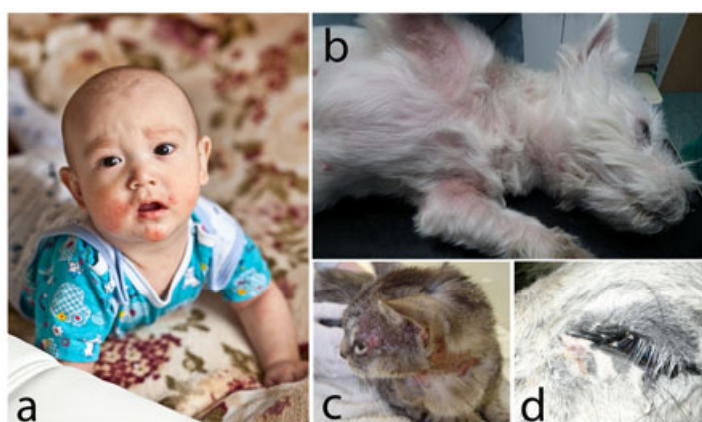
Figure legends

Figure 1: Comparing symptoms associated with food adverse reactions in atopic humans, dogs, cats and horses. a) An atopic toddler may suffer from food allergy, especially to milk and egg, resulting in inflammatory eruptions at food contact sites in particular, as illustrated here. From Fotolia.com©Garevskaya Elina. b) In dogs, AFR may clinically manifest as cutaneous abnormalities, indistinguishable from those of atopic dermatitis. A West Highland White Terrier is shown with itchy atopic eczematous lesions subaxillary and in the face. Kindly provided by ©Lucia Panakova, Div. of Veterinary Dermatology, University of Veterinary Medicine Vienna, Austria. c) Cats with food allergy

may show cutaneous symptoms. An Abyssinian cat suffers from allergic pruritus of the head and neck, leading to scratching, excoriations and possibly superinfections. Picture kindly provided by ©Lucia Panakova, Div. of Veterinary Dermatology, University of Veterinary Medicine Vienna, Austria.

d) Food allergy in horses is less defined, but atopy is an important risk factor also in equine AFRs. In this horse, a periorbital lichenoid atopic lesion is shown. Picture kindly provided by ©Jan Rybníček, Veterinary Dermatology & Dermatopathology Service, Oslavany-Ivancice, Czech Republic.

Figure 2: Diagnostic work-up of food allergy in human and veterinary patients. *) In allergic diseases of humans, dogs, cats and horses a careful anamnesis (incl. a food diary and consideration of ancillary factors) in context with the clinical picture is of utmost importance. A differential diagnosis to rule out other reasons for symptoms besides allergy has to be performed in all species. **) An atopy patch test in humans could reveal information on late phase (type IV) reactions, when skin prick test and specific serum IgE test render no positive results. ***) The correlation of IDT and serum IgE with clinical reactivity is poor. Diagnosis of food allergy in dogs and cats by default is made via elimination diet. ****) A patch test in dogs can help with the choice of ingredients for the elimination diet. *****) In healthy horses, false-positive results are often obtained from IDT and measurement of specific IgE. Figure modified from (40).



Pali-Schöll
Figure 2

