Allergy to Fungi in Veterinary Medicine

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The fungal kingdom comprises ubiquitous forms of life with 1.5 billion years, mostly phytopathogenic and commensals for humans and animals. However, in the presence of immune disorders, fungi may cause disease by intoxicating, infecting or sensitizing with allergy. Species from the genera *Alternaria*, *Aspergillus* and *Malassezia*, as well as dermatophytes from the genera *Microsporum*, *Trichophyton* and *Epidermophyton*, are the most commonly implicated in veterinary medicine.

allergy Alternaria Aspergillus dermatophytes fungal allergens immunocompetence indoor/outdoor allergens Malassezia

1. Introduction

Fungi are living forms and have evolved for approximately 1.5 billion years [1]. Fossil evidence of fungi is scarce, probably because of their easily disrupted soft body nature, frequent microscopic dimension and morphology difficult to distinguish from those of other microbes [2]. The majority of fungal organisms are saprophytic, lacking pathogenicity to plants, humans or animals. However, a small proportion of species may become pathogenic, affecting plants, humans and animals by producing toxins, infecting or causing allergy in humans and animals. Between the genera Alternaria, Mucor, Aspergillus and Fusarium [3], as well as Trichophyton and Microsporum [4], may be found the most frequently involved pathogenic fungal species to plants, humans and animals. Several of the species comprised in those genera are able to cause considerable economic losses to agriculture, with relevant loss of food for consumption, and serious diseases in humans and animals, especially in immunocompromised individuals [3], a Species from the fungal kingdom can be found almost everywhere. Fungal species evolved side by side with other live beings as decomposers of organic matter. By secreting enzymes into their environment, fungal species can extract the available nutrients, mostly carbohydrate metabolites, from other organisms as they are heterotrophic. Other nutrients, such as proteins and lipids, are also digested for subsequent fungal absorption, and in the end, the environment becomes full of the leftovers from fungal digestive proteins. Successively, fungal environmental spread happens through airborne dissemination of spores, hyphae and hyphal fragments, as well as those leftover, reaching almost all places on earth [5].

2. Most Relevant Fungi in Health

The *Aspergillus genus* comprises several of the most common fungal species (e.g., *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans and Aspergillus terreus*) involved in respiratory infection,

most often in birds, and it may cause large economic losses in the poultry industry [6]. A recent study by Cheng et al. (2020) [7] highlighted the role of Toll-like receptors (TLR) in the mediated innate immune response associated with *A. fumigatus* infection in chickens, triggering a massive production of several pro-inflammatory cytokines, which leads to severe airsaculitis and infiltrative and granulomatous pneumonia. Species from the genus *Aspergillus* are also involved in respiratory allergies, such as allergic bronchopulmonary aspergillosis, allergic *Aspergillus* sinusitis, IgE-mediated asthma or hypersensitivity pneumonitis [8][9]. These situations may derive from primary sensitization to *Aspergillus* airborne compounds, either indoors or outdoors [3].

The Alternaria genus comprises several phytopathogenic species, affecting the quality of grains, as well as different vegetables, such as tomatoes and peppers, and consequently their economic value [3]. Alternaria species also produce several types of cytotoxic and teratogenic mycotoxins, known to block the synthesis of sphingolipid, by inhibiting the rate-limiting enzyme, ceramide synthase [10], which may also compromise the integrity of the skin barrier [11]. Despite less frequently than Aspergillus, Alternaria is also known for its ability to cause onychomycosis, even in healthy individuals [12], but worse conditions may occur in immunocompromised individuals, where skin infections [12][13], keratomycosis [14] or sinonasal infections may be observed [15].

Sensitization to *Alternaria* fungus is also common, with species from this genus as the most frequently associated with type I hypersensitivity, which has been related to exposure in the indoor and outdoor environment, mostly in warm climates [16][17].

Species from the *Fusarium* genus commonly grow on cereal, contaminating the grains with toxins and making them unsafe for consumption [3][18]. Concerning the repercussion on human and animal health, *Fusarium* may disturb the immune system, either by immunotoxic impairment or sensitization with allergy. Aside from the toxic effects, allergic consequences were also reported, such as bronchial asthma, allergic alveolitis and rhinitis, atopic conjunctivitis, organic dust toxic syndrome and chronic fatigue-like syndrome [19]. There are several *Fusarium* allergens, some of them known for cross-reacting to each other [20]. *Fusarium* species are also known for their ability to infect either immunocompetent or immunocompromised individuals [21]. *Fusarium solani*, for instance, contains several allergens that were found to be reactive with serum from patients sensitized to many fungi [22].

Curvularia is a relevant genus comprising at least 40 saprophytic species, but only a few of those are known for their capacity to become phytopathogenic. These species produce several mycotoxins with cytotoxic activity as curvulins and brefeldins [3]. Brefeldin A is, in fact, used for that property as a blocker of the intracellular cytokine transport in different immunological studies [23]. Moreover, *Curvularia lunata* was reported to cause eye and skin infections upon trauma [24], as well as onychomycosis, skin ulcerations and subcutaneous mycetoma [25]. *Curvularia* may also sensitize human individuals, causing especially respiratory signs [26] and showing marked cross-reactivity with *Alternaria alternata* and *Epicoccum nigrum* [27][28]. Dogs were also reported to have either infection by *Curvularia* fungi [29] or allergy upon sensitization to their allergens [30].

Cladosporium is a ubiquitous genus and can be isolated from different materials, such as organic matter, soil, straw, textiles and even ink. It may damage fresh vegetables and fruits, producing great economic losses [3]. Infection by *Cladosporium* fungi has been reported in several species, such as humans, dogs [31], horses [32] and cats [33][34]. Furthermore, allergic conditions associated with *Cladosporium* are currently referred to in humans [3][35] and dogs [36].

Mucor and *Rhizopus* are two other genera belonging to the Mucorales group, comprising pathogens of plants [3] that may also affect humans, mainly immunosuppressed individuals [37], as well as allergic individuals, either humans [16] or animals [30][38][39].

Another relevant fungal group of diseases is dermatophytosis. This zoonosis is mainly caused by fungi from the genera *Microsporum*, *Trichophyton* and *Epidermophyton* and is rather common among humans and animals attending dermatological consultation, frequently affecting immunocompetent individuals. The prevention and treatment of dermatophytosis rely on good sanitation and hygiene, as well as on specific treatment. It is frequently called the ringworm disease for its round-shaped skin lesions and, besides the etiotropic therapy, vaccination with the first generation of live attenuated preparations have allowed successful control and even eradication when large numbers of cattle and fur-bearing animals were affected [40][41].

The genus *Candida* comprises over 200 species, mostly integrating the normal human and animal microbiota, being considered as commensals but facultatively pathogenic. Only 15 have been isolated from human and animal infections, with *Candida albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* as the most common pathogenic species. Different domestic and sylvatic species (e.g., birds, cats, dogs, horses, pigs and ruminants) have been diagnosed with candidiasis, affecting several organic departments besides mucosa or skin [42]. Unlike malasseziosis, candidiasis is a rare infection in animals but may also occur associated with atopy as well as to other mostly immunosuppressive disorders [43][44]. However, disseminated candidiasis without apparent predisposition has been reported [45].

3. Fungi as Sources of Allergens

Allergy to *Dermatophyte* fungi has also been reported. Several allergens from the genus *Trichophyton* have been identified with evidence of *Trichophyton*-related IgE-mediated asthma in humans. In an individual, the same antigens that do not elicit immediate hypersensitivity may nevertheless trigger delayed-type hypersensitivity. Based on the observation of acute vs. chronic skin infection, delayed responses appear to confer protection, while immediate ones do not. Amino acid sequence identity of *Trichophyton* allergens suggests a dual role of these proteins for fungal pathogenesis and allergic etiopathogeny. Some T-cell epitopes have been mainly associated with delayed hypersensitivity, which may be useful for the development of rather effective peptide vaccines, allowing better control of *Trichophyton* infection and related allergy [46].

Regarding sensitization and possible subsequent allergy, fungal spores are between the first substances found as sensitizing to humans, following contact in indoor or outdoor environments. The sensitization to fungal species

commonly represents more than 5% of the general population but reaches higher rates in atopic individuals. Exposure to fungal allergens may occur by contacting intact spores and mycelia or their fragments. Spores in germination are known for presenting a wider allergen range. Studies on the genus *Alternaria*, probably the most studied from all allergenic fungi, have been very helpful in terms of the effect of common long-term low-level fungal exposure. Fungal exposure does not mean sensitization or any other pathology, as demonstrated when the exposed population did not include atopic individuals. In fact, indoor fungal exposure and respiratory disease are frequently associated with an atopic predisposition [16] or immune-compromising conditions [3].

Sensitization to *Alternaria* has been estimated to be 7%, while 6% to *Aspergillus* [47], but considering the occurrence of subclinical sensitization, those figures may be underestimated. Furthermore, sensitization to fungi is a considerable cross-reactive condition. Hence, contact with primary sensitization to a limited number of fungal species could result in sensitization to a wide variety of other fungal species, as it was suggested when 6565 individuals with positive IgE in at least one fungal test were tested with a larger battery of fungal species, showing positive to all, in 1208 cases [48]. In fact, fungal proteins sharing homologous structural elements and similar functions showed marked cross-reactivity [49][50]. Fungal structure-derived particles may become aerosolized in concentrations 300–500 times greater than spores [51], which may potentiate contact, leading to possible sensitization.

Thus far, in Allergome—allergen database (http://www.allergome.org/, accessed on 20 January 2022)—there are 1024 registrations for “fungi” out of 7535 entries. Approximately half of those refer to *Alternaria* with 309 and *Aspergillus* with 195, with respectively 186 and 142 allergens, including isoforms [52]. This makes *Alternaria* the most relevant fungal genus for allergies by far. It is the fungus with the most sensitized humans and the one with the highest association with asthma deaths [53].

Fungi may present the highest concentration of airborne allergen particles, but there is evidence that increased exposure to indoor microbial diversity, including fungi, may represent a protective issue regarding the occurrence of atopy [16], falling into the paradigm of the hygiene hypothesis [54]. Regarding the prevalence of airborne fungi, in northern regions, the amount of fungal spores per cubic meter of outdoor air is usually low during Spring, rising with rainfall and with temperature until a peak during Autumn (around 50,000/cubic meter of air), while in southern regions levels tend to stay more constant, around tens of thousands, varying according to environmental humidity [55]. Regarding the indoor concentration of fungi spores, it usually correlates with outdoor figures, despite major genera, such as *Chaetomium* and *Stachybotrys,* not correlating with outdoor concentrations. Furthermore, major genera associated with the indoor environment, such as *Aspergillus* and *Penicillium*, also do not correlate as much with outdoors as *Cladosporium* and *Alternaria* [56].

Regarding mold, or even house-dust mites and insect allergens for animals, especially dogs and horses, there are not many reports, and major allergens may also differ from those to humans. Despite the evidence of sensitization to mold allergens in dogs, leading to atopic dermatitis, the reported sensitization rate is different between studies, which may be due to a low level of standardization of allergen extracts, resulting in poor specificity of the assays [57].

In equine, recurrent airway obstruction (RAO) has been associated with exposure to moldy hay. Despite sensitization to fungi and aggravation of clinical signs following contact with moldy hay or challenges with mold extracts, only non-IgE-mediated mechanisms have been implicated in the pathogenesis of RAO. However, basophil histamine-releasing test upon stimulation with fungal allergens showed higher in horses with RAO than in healthy individuals [58]. In fact, increased *Aspergillus fumigatus*-specific IgE and IgG responses were found in the bronchoalveolar lavage fluid of RAO-affected horses, following in vitro provocation with fungal extracts [59]. Specific IgE to recombinant allergens, such as Alt a 1 and Asp f 7, 8 and 9, was mostly detected in bronchoalveolar lavage and serum from RAO-affected individuals, despite no difference in specific IgE to fungal extracts between healthy and affected horses. Specific IgG to *Aspergillus fumigatus* has been detected in both healthy and RAO-affected individuals, but the latter were found to have higher IgG levels than Asp f 8 [60][61]. Despite the lack of knowledge about which proteins are major allergens for horses, significant differences in specific IgE against Asp f 7 were found between RAO-affected and healthy individuals. In a study by Scharrenberg et al. (2010) [62], those kinds of differences were only observed in the offspring from one stallion, suggesting a genetic predisposition to sensitization and allergy. In fact, the genetic evaluation identified different quantitative trait loci associated with RAO.

A study Carried out by Leocádio et al. (2019) [63], in a population of 21 horses with a compatible clinical history of allergy, revealed positive intradermal tests (IDT) for *Alternaria alternata*, *aspergillus fumigatus* and a fungi mix in, respectively, nine, five and five individuals. The determination of serum-specific IgE revealed positive to *Aspergillus fumigatus* in four individuals, but no concordance was observed with previous IDT [64].

Relevant mold allergome for dogs or cats has not been clarified yet, and recombinant mold allergens have not been used for diagnostic purposes in these species. For horses, there are already a few mold allergens identified, but a significant rate of recognition to point out the major allergens is still not established [57].

Regarding the nature of immune response against antigenic structures, it is necessary to have in mind that all body epithelial barriers represent ecosystems in which the microbiota (bacteria, fungi and viruses) find nutritive conditions to multiply. These surfaces are consequently highly populated by those producing several metabolites that influence the host immune system, inducing either tolerance or triggering defensive mechanisms as sensitization, sometimes leading to allergy. Healthy immunity relies on a good equilibrium between the microbiota and host defense system, simultaneously preventing invasion by pathogens and avoiding host overreaction. For this purpose, two opposite pathways—immune activation by microbial metabolites and immune regulatory processes—constantly stand in a tiny equilibrium [65]. With regard to animal atopic dermatitis, defects in the lipid and protein constitution of the skin, aggravated by inflammation, may contribute to the impairment of the barrier function, favoring the deep penetration of allergens, with stimulation of the immune response. On the other hand, if a marked genetic predisposition to develop a Th2 kind of immune response is present, even a low epidermal penetration of allergens may trigger sensitization with subsequent allergy. This dual condition is currently designated by the outside/inside–inside/outside paradigm [11].

The highest concentration of immune resources is found in the gastrointestinal tract, where a rich mix of commonly commensal bacteria, archaea, fungi and viruses is found. Therefore, its role in the host health/disease equation is crucial but poorly understood [66]. The human gastrointestinal tract is recognized as the first barrier towards food-derived contaminants, including a large variety of xenobiotics. The gastrointestinal tract immune system must face all the related challenges to keep the mucosal barrier up, supporting its structural integrity [67]. Ironically, despite mycotoxin action possibly affecting immune response, *Alternaria alternata* toxins may also contribute to the epithelial barrier function by activating the aryl hydrocarbon receptor pathway [68]. Neonatal gut increase in particular fungi, such as *Candida* and *Rhodotorula*, with a decrease in bacteria, such as *Bifidobacterium*, *Akkermansia* and *Faecalibacterium*, has also been associated with a reduction in T cell expression of Foxp3, CD25 and CD4, leading to an increased risk of childhood atopy [69].

Regarding the genus *Candida*, the Allergome platform presents 21 identified allergens out of 7535 entries [52]. Eleven of those are specifically from *C. albicans*, but to the author's knowledge, no allergens have been associated with possible animal sensitization to *Candida* species.

For diagnostic skin testing, commercial whole-allergen extracts usually vary in the content of major and minor allergens, compromising the reproducibility of the results. Molecular allergens (naturally purified or recombinant) have been produced for nearly all relevant allergen sources, such as pollens, mites, fungi, *Hymenoptera* venom and different foods, and can be used for diagnosis [70]. For veterinary allergy diagnosis, IDT is the first choice complementary method and most suppliers present well-defined concentrations for their allergen extracts. However, standardization is still a relevant issue when aiming for the reproducibility of results [71]. The current, most relevant information regarding sensitization and allergy to fungi in veterinary medicine is summarized in **Table 1**.

Table 1. Summary of the current, most relevant information on the sensitization and allergy to fungi in veterinary medicine.

Sensitizing Species	Allergens/Molecular Weight (kDa)	Relevant for	Recommended Extract Concentration/mL	References
Alternaria alternada	Alt a 1 (30)	Dog; horse	1000–8000 PNU(#)/100 µg(##)	[59][63][72]
Aspergillus fumigatus	Asp f 7 (27.4); Asp f 8 (11); Asp f 9 (34)	Dog; horse	1000–8000 PNU(#)/100 µg(##)	[59][60][61][62][63][64]
Malassezia sp.		Dog	100 µg (##)	[72][73][74][75][76][77][78]
Malassezia globosa	MGL_1304 (26)	Horse		[61]
Aspergillus mix (*)		Dog; horse	1000–8000 PNU(#)/100 µg(##)	[63][72]

Sensitizing Species				
	Allergens/Molecular Weight (kDa)	Relevant for	Recommended Extract Concentration/mL	References
Fungi mix (**)		Dog; horse	1000–8000 PNU(#)/100 µg(##)	[63][72]

(*) Extract mix of *Aspergillus flavus*, *A. fumigatus*, *A. nidulans* and *A. niger* (Nextmune, Lelystad, Nederlands). (**) Extract mix of *Alternaria alternata*, *Aspergillus fumigatus* and *Cladosporium herbarum* (Nextmune, Lelystad, Nederlands); (#) Protein Nitrogen Units; (##) Extracts from Nextmune, Lelystad, Nederlands.

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