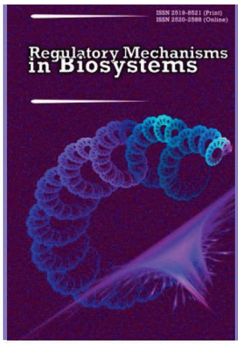

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Sensitivity patterns to fungal allergens in the population of Vinnytsya region

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Fungi are ubiquitous living beings present in the indoor and outdoor environment. Spores and mycelium of fungi carried by air have a great impact on ecology, the economy, in particular on agriculture, as well as on human health. It has been established that the incidence of fungal pathologies has increased rapidly over the past two decades. Fungi can cause allergies, and can be infectious agents, especially in immunocompomised people. Fungal spores are powerful sources of allergenic molecules covering a wide range of biochemical classes. Together with the fungal mycelium, they can cause the development of hypersensitivity, which is one of the most common pathological immune responses. Currently, known fungal aeroallergens are found in 3 fungal classes – Basidiomycota, Ascomycota, and Zygomycota. Therefore, the goal of our work was to determine the level of sensitivity to fungal allergens in the population of Vinnytsya region in order to prevent allergies caused by fungi. Data analysis of IgE-mediated, genuine, sensitization to fungal allergens of *Alternaria* (Alt a 1, Alt a 6), *Cladosporium* (Cla h, Cla h 8), *Aspergillus* (Asp f 1, Asp f 3, Asp f 4, Asp f 6), *Penicillium* (Pen ch), *Malassezia* (Mala s 11, Mala s 5, Mala s 6) and *Saccharomyces* (Sac c) was carried out using a component-resolved allergy diagnostics by ALEX2 test. The data of 87 residents of the Vinnytsya region aged 1 to 66 who underwent molecular allergy diagnostics in 2020–2022 were taken into account. Sensitivity to fungal allergens was observed in 20 patients or 23.0% of those tested. Among them, the highest level of sensitivity, in 15 patients or 75% of the number of sensitive individuals, was observed for the *Alternaria* fungus. The allergen component Alt a 1 caused high and very high levels of sensitization in 3 and 7 patients, respectively. Sensitivity to *Aspergillus* and *Malassezia* had the second highest rate: 6 patients or 30% of sensitized individuals were sensitive to these two fungal allergens. *Alternaria* was the most important fungal agent causing sensitization of the examined population of Vinnytsya region. *Aspergillus* allergens, known for their ability to cause both allergic and infectious reactions, were next in clinical importance. *Cladosporium*, which usually produce a highest number of spores in the atmosphere among all fungi, was characterized by low allergenicity. High levels of both specific and total immunoglobulin E can be prognostic markers of clinical manifestations of fungal allergy. This information should be taken into account for the prevention of fungal allergy among the population when creating allergy forecasts.

Keywords: fungal allergy; allergic sensitization; component-resolved allergy diagnostics; *Alternaria*; *Malassezia*; *Aspergillus*.

Introduction

Fungi are common microorganisms present in the outdoor and indoor environment. These organisms are able to synthesise organic matter from carbon dioxide and use the finished organic compounds to support their vital activity. By emitting gaseous compounds and releasing spores into the environment, they can affect human health. The gaseous products they emit can be toxic, and the spores they release can be poisonous or allergenic (De Linares et al., 2022, 2023).

Almost all people are exposed to fungi. It has been established that the incidence of fungal pathologies has increased rapidly over the past two decades (Celakovská et al., 2018; Luo et al., 2020; Hu et al., 2021). Fungi can cause allergies and can also be infectious agents, especially in people with compomised immune systems. The immune response performs not only protective functions, but under certain conditions can also be the cause of certain pathological processes.

One of the most common health problems worldwide is fungal allergy. In particular, fungal spores are powerful sources of allergenic molecules covering a wide range of biochemical classes (Celakovská et al., 2018; Luo et al., 2020; Hu et al., 2021). It is they, as well as fungal mycelium, that cause the development of hypersensitivity, one of the most common manifestations of pathological changes caused by the immune response. After all, fungi can simultaneously cause infectious and severe allergic reactions, promoting type I (IgE), type III (IgG) and type IV (T cells) hypersensitivity. Humoral factors, such as antibodies, or cellular factors, such as sensitized T lymphocytes, play a major role in the mechanisms of hypersensitivity reactions. Type I hypersensitivity develops immediately within 10–30 minutes and is recorded mainly in patients with atopy, while infections are often associated with immune deficiency. The main participant in an immediate type (type I) allergic reaction is immunoglobulin class E (IgE). There is a specific immunoglobulin E for each allergen.

Immediate reactions which are supplied with high levels of IgE are "atopic". Atopic diseases are characterized by smooth muscle spasm, hyperaemia and swelling, and changes in the secretory activity of certain glands. Atopic diseases include bronchial asthma, urticaria (hives), anaphylaxis, allergic dermatitis and rhinitis, etc.

Hypersensitivity to the allergen is the main condition for the sensibilization and further development of immediate response. The peculiarity of allergens, including fungal ones, is the ability to induce the production of specific homocytotropic antibodies. They are immunoglobulin class E. They adhere to the surface receptors of mastocytes, basophils, eosinophils and trigger allergic reactions.

Fungal allergens enter the body in various ways – through the respiratory system, digestive tract, skin and as a result of infectious processes. Their activity depends on the properties of the allergen itself and the body condition (Goode & Marczylo, 2023).

The known fungal aeroallergens are currently found among the representatives of 3 fungal divisions: Basidiomycota, Ascomycota and Zygomycota (Levetin et al., 2016).

Airborne Ascomycota allergens are the most numerous: the division contains almost 50% of all named fungal species. It includes ~80% of fungi that are medically important (Murray et al., 2021). The currently known allergens belonging to Ascomycota include 95 molecules that elicit an IgE response; 91 of them are airway (Allergen nomenclature. WHO/IUIS Allergen Nomenclature Sub-Committee. http://allergen.org/search.php?TaxSource=FungiAscomycota). The Basidiomycota includes 23 known allergens. Only 10 of them are airborne (Allergen nomenclature. WHO/IUIS Allergen Nomenclature Sub-Committee. http://allergen.org/search.php?TaxSource=FungiBasidiomycota). In Zygomycota, only 2 allergens (Phi o 1 and Phi o 2) have been isolated to date, and both of them are airborne (Allergen nomenclature. WHO/IUIS Allergen Nomenclature Sub-Committee. http://allergen.org/ search.php?TaxSource= FungiZygomycota).

The most common cause of allergic diseases are spores and mycelium of ascomycotic fungi of the genera *Alternaria*, *Cladosporium*, *Aspergillus* and *Penicillium* (Wardlaw et al., 2021).

Xerophilic species of *Penicillium* and *Aspergillus*, with the exception of *Aspergillus fumigatus*, cause allergic diseases as indoor allergens (Palmieri et al., 2022; Rozaliyani et al., 2023).

The concentration of *Penicillium* spores in premises increases with insufficient heating and ventilation, poor lighting, and the presence of pets (Sharpe et al., 2014; De Linares et al., 2023). Also, high concentrations of this type of fungi increase the risk of developing obstructive disorders and bronchial asthma in children (Wardlaw et al., 2021).

The genus *Aspergillus* includes more than 100 species that are ubiquitous and is the main representative of the Ascomycota, It poses both an infectious and allergic threat to humans (Vitte et al., 2022). Fungi of this species have a high ability to colonize the bronchial tract of asthma patients, causing severe persistent asthma and reduced lung function, and sometimes leading to allergic bronchopulmonary aspergillosis (Bhankhur et al., 2019; Wardlaw et al., 2021).

The presence of *Aspergillus* fungi in the air is a major risk factor for diseases such as bronchial asthma, allergic rhinitis, rhinosinusitis, allergic bronchopulmonary aspergillosis, hypersensitive pneumonitis, aspergilloma, and invasive aspergillosis (Agarwal et al., 2019; Bhankhur et al., 2019). Currently, a large number of major allergens of the genus *Aspergillus* have been isolated. The most clinically important allergens are Asp f 1, Asp f 2, Asp f 3, Asp f 4, Asp f 6 (Caraballo et al., 2020).

In particular, *Aspergillus fumigatus*, which is a thermophilic fungus, poses both an infectious and allergic threat to humans (Vitte et al., 2022; Bouyssi et al., 2023). It has a high capacity to colonise the bronchial tract of asthma patients, causing severe persistent asthma and reduced lung function, and sometimes leading to allergic bronchopulmonary aspergillosis (Bhankhur et al., 2019; Wardlaw et al., 2021).

Mesophilic fungi (*Alternaria alternata*, *Cladosporium herbarum*) act only as aeroallergens (Aguilera et al., 2022; Hughes et al., 2022), and sensitization and exposure to species of these genera are associated with the development of asthma and rhinitis (Bhankhur et al., 2019).

Alternaria spp. are usually classified as environmental fungi, but they can also occur indoors, especially in highly humid environments (e.g. baths) (Abel-Fernández et al., 2023). The main allergen of *Alternaria* spp. is Alt a 1, which is localised in the spore cell wall. This fact may explain its high importance as an airway allergen (Twaroch et al., 2012). *Alternaria alternata* is one of the main environmental allergens associated with the development of bronchial asthma. To date, 12 allergens of *A. alternata* have been described (Allergen nomenclature. WHO/IUIS Allergen Nomenclature Sub-Committee. http://allergen.org/search.php?Species= *Alternaria alternata*). It is Alt a 1 that is the main allergen and marker of genuine sensitisation to *A. alternata*, being mainly involved in the development, course and severity of asthma (Allergy&Autoimmune disease. The Allergen Encyclopedia. www.thermofisher.com/diagnostic-education/hcp/wo/en/resource-center/allergen-encyclopedia/allergen-component.html?key=m229).

One of the most common genera of moulds is *Cladosporium*. Similarly to *Alternaria* spp., it lives mainly outdoors, but is also found in enclosed spaces (Grinn-Gofroń et al., 2019; Wardlaw et al., 2021; Sauliene et al., 2023). Its clinical significance is similar to that of *Alternaria* spp. Although a large number of *Cladosporium* spp. proteins have been isolated, none of them is a major allergen. All identified allergens are minor allergens, i.e., they cause sensitization in a small number of patients and have cross-sensitisation (Almeida et al., 2018; Vélez-Pereira et al., 2023).

Lipophilic yeasts of the genus *Malassezia sympodialis* colonize the skin of both asthmatic patients and healthy individuals, causing IgE-mediated sensitization in patients with asthma (Pedrosa et al., 2018; Rhimi et al., 2020; Hobi et al., 2022). Such fungi have pathogenic potential and can cause skin diseases through various mechanisms: activation of the immune system (for head and neck dermatitis), eczematous/inflammatory reactions (seborrhoeic dermatitis), infection of the stratum corneum (tinea pedis) (Saunte et al., 2020; Celakovska et al., 2021).

Therefore, the aim of our study was to determine the level of sensitivity to fungal allergens in the population of Vinnytsya region in order to prevent fungi-caused allergies.

Materials and methods

To solve the tasks set, we analysed the data of IgE-mediated, genuine sensitization to fungal allergens available for evaluation in the multiplex molecular test ALEX2, which makes it much easier to find the main and cross-reactive allergens (Allergy Explorer (ALEX®; MacroArray Diagnostics, Wien, Austria) (Heffler et al., 2018; Celakovska et al., 2021).

The test panel includes allergens from such fungi as *Alternaria* (Alt a 1, Alt a 6), *Cladosporium* (Cla h, Cla h 8), *Aspergillus* (Asp f 1, Asp f 3, Asp f 4, Asp f 6), *Penicillium* (Pen ch), *Malassezia* (Mala s 11, Mala s 5, Mala s 6), yeast (Sac c.).

The levels of sensitivity of patients to fungal allergens were determined in accordance of the IgE levels: < 0.3 kUA/L – negative or undetectable IgE level; 0.3 – 1 kUA/L – low IgE level; 1 – 5 kUA/L – medium IgE level; 5 – 15 kUA/L – high IgE level; > 15 kUA/L – very high IgE level.

Data from 87 residents of Vinnytsya region aged 1 to 66 years who underwent molecular allergy diagnostics in 2020–2022 were used for the evaluation.

Results

The analysis of the data showed that sensitivity to fungal allergens was observed in 20 patients or 23.0% of the tested individuals.

Of these, the highest level of sensitivity was observed to *Alternaria* fungus – in 15 patients or 75% of the sensitive individuals. In turn, 14 patients, or 93.3%, were sensitive to the major component of *Alternaria* protein Alt a 1, one of whom was also sensitive to the minor allergen Alt a 6. Another patient was sensitive only to the Alt a 6 allergen.

The allergenic component Alt a 1 caused a high and a very high levels of sensitization in 3 and 7 patients, respectively.

Sensitivity to *Aspergillus* and *Malassezia* was in the second place. These two fungal allergens caused sensitivity of 6 patients or 30% of sensitized individuals. In 1 patient, a high level of sIgE sensitivity to the allergenic component Asp f 4 was recorded. Instead, 2 patients had a high level of sensitization to the allergenic component Mala s 6. Among those sensitive to *Aspergillus*, 4 patients were also co-sensitized to *Alternaria*.

Among the people sensitive to *Malassezia*, one patient was co-sensitized to *Alternaria*, *Aspergillus*, and *Cladoporium*, and another one – to *Alternaria* and *Aspergillus*. Two other patients were sensitive only to *Alternaria* allergens and 2 were not sensitive to any other fungi.

Sensitization to *Cladosporium* was characteristic of only 2 patients or 10% of the study sample. As it is already mentioned, one of these patients was co-sensitized to *Alternaria*, *Aspergillus* and *Malassezia*. The other was co-sensitized to *Alternaria* only.

Only 1 person was sensitive to *Penicillium*, which accounted for 5% of those sensitized. This person was not sensitive to any other fungal allergen available for the analysis. No people were found to be sensitized to Sac c yeast extract. For the allergenic components of the fungi *Alternaria* (Alt a 6), *Aspergillus* (Asp f 1, Asp f 3, Asp f 6), *Cladosporium* (Cla h, Cla h 8), *Malassezia* (Mala s 11, Mala s 5), and *Penicillium* (Pen ch), only low and medium levels of patient sensitivity were observed. The highest mean IgE levels in sensitized individuals were recorded for the allergenic components of Alt a 1, Mala s 6, Asp f 4 and Asp f 3. There, levels were 13.84, 0.91, 0.62 and 0.38 kUA/L, respectively. The mean level of total IgE was 828.29 kUA/L. It ranged from 19.19 to 2819.00 kUA/L with a median value of 523.00 kUA/L. The mean sIgE value was above the threshold of 0.31 kUA/L for Alt a 1 (13.84 kUA/L), Asp f 3 (0.38 kUA/L), Asp f 4 (0.62 kUA/L) and Mala s 6 (0.91 kUA/L) (Table 1).

Table 1
sIgE levels of patients sensitive to fungal allergens

Patient	sIgE to allergenic components of fungi, kUA/L										Total level (tIgE) in sensitized individuals, kUA/L
	Alternaria		*Aspergillus*		*Cladosporium*		*Malassezia*		*Penicillium*		
	Alt a 1	Alt a 6	Asp f 3	Asp f 4	Cla h	Cla h 8	Mala s 11	Mala s 5	Mala s 6	Pen ch	
1	14.46	0	0	0	0	0.05	0.02	0	0	0	90.00
2	41.90	0	0.31	0	0	0	0	0	0	0	105.00
3	42.87	1.13	4.18	0.20	1.09	0.42	0	0	0.68	0	2565.00
4	0	0	0	0.06	0.09	0	0	0	0	0.34	1471.00
5	0	0	1.89	9.06	0.21	0.13	0	0	0	0	1024.00
6	0.63	0	0	0	0	0	0	0	0	0	264.00
7	0.42	0	0	0	0	0	0	0	0	0	99.00
8	0	0	0.33	2.57	0.25	0	0	0	0	0	1667.00
9	40.91	0	0.65	0	0	0	0	0	0	0	136.00
10	32.56	0	0	0	0	0.45	0	0	0	0	96.00
11	0	0	0	0	0	0	3.55	0	10.83	0	887.00
12	0	0.50	0.01	0.48	0	0.07	0.05	0	5.63	0	2819.00
13	11.29	0	0	0	0	0	0	0.42	0	0	19.19
14	0	0	0	0	0	0	0	0.32	0	0	539.00
15	27.37	0	0	0	0	0	0	0	0	0.02	27.37
16	5.46	0	0	0	0	0	0	0	0	0	<20.00
17	34.80	0	0.28	0	0	0	0	0	0.99	0	1063.00
18	2.77	0	0	0	0	0	0	0	0.02	0	523.00
19	19.89	0	0	0	0	0	0	0	0	0	149.00
20	1.50	0	0	0	0.10	0.12	0	0	0	0	2194.00
AVG sIgE	13.84	0.08	0.38	0.62	0.09	0.06	0.18	0.04	0.91	0.02	828.29
Median	4.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	523.00

Discussion

The data on the sensitization of the population are in a good accordance with the results of our previous studies for Ukraine (Rodinkova & Jurjev, 2019; Rodinkova et al., 2022). According to these studies, the main allergenic component of the fungal kingdom is *Alternaria*. The overall sensitivity to it in the Ukrainian allergic population ranges from 23 to 25%. Such a high level of sensitivity may be due to the fact that *Alternaria* is a ubiquitous fungus that reproduces in the environment, in particular, on dying vegetation (Leite et al., 2023).

Cladosporium that produces the largest number of spores and can live both outdoors and indoors, in particular in bathrooms, is generally low-allergenic (Grinn-Gofron et al., 2020; Kasprzyk et al., 2021; Charalampopoulos et al., 2022). This is confirmed by our studies too.

However, the results we obtained on sensitisation to *Aspergillus* and *Malassezia* are interesting taking into account possible ways of human contact with these fungi. After all, *Aspergillus* often settles indoors and can provoke the development of both allergic sensitisation to it and infectious diseases. *Malassezia*, in turn, is better known as a fungus that provokes human dermatomycoses – infectious skin diseases (Morand et al., 2019; Rhimi et al., 2020; Abdillah & Ranque, 2021). However, in the described cases, it should be borne in mind that either *Aspergillus* or *Malassezia* can be both infectious and allergic agents for the patient.

Quantitative determination of specific IgE antibodies allows one to assess the relationship between their level and clinical manifestations of allergy. Low values of this indicator specify a low probability of developping a clinical stage of an allergic disease, while high levels have a high correlation with severe manifestations of the disease. If high levels of specific IgE are detected, it is possible to predict the development of allergies in the future and the likelihood of its symptoms (Mokhtar et al., 2023).

The high levels of total immunoglobulin E (tIgE) found in the present study may be a good predictive marker of an allergic reaction in both adults (Cameron & Luo, 2023) and children (Lin et al., 2021), as the concentration of allergen-specific IgE correlates with the likelihood of symptoms (Mokhtar et al., 2023). In particular, the higher the level of tIgE, the higher the likelihood of clinical manifestations of sensitization to *Alternaria* (López Couso et al., 2021). Also, a high level of total IgE, more than 1000 kUA/L, is indicated as one of the diagnostic criteria for bronchopulmonary aspergillosis caused by *A. fumigatus* (Agarwal et al., 2022). A particularly useful tool for diagnosing allergy in children is the level of total immunoglobulin E in the serum (Lin et al., 2021).

Prevention of these diseases is important, given the social significance of diseases resulting from contact of the human body with fungal particles. First of all, it consists in identifying the causative allergens and further preventing contact with them (Rodinkova, 2002). Preventing such contact can be achieved, among other things, by alerting the public to clinically significant concentrations of airborne fungal allergens via the allergy forecasting system (Rodinkova, 2013; Scevkova & Kovac, 2019).

In addition, to prevent the development of diseases caused by fungi, public health professionals, medical mycologists, pharmacists and diagnosticians should focus on improving the overall laboratory diagnostic capacity and surveillance, and increasing investment in research and innovation, which in turn will lead to improved epidemiology (Burki, 2023).

In this context, the use of the ALEX test can significantly expand the diagnostic capabilities to check the patients' sensitization to various groups and types of allergens and allergenic components. This significantly improves the accuracy of allergy diagnosis.

Conclusions

Alternaria was the most important fungal agent causing sensitisation of the tested population of Vinnytsya region. *Aspregillus* allergens, known to cause both allergic and infectious reactions, were the next most important allergens in terms of clinical significance. *Cladosporium* which usually has the highest number of spores in the air is characterised by low allergenicity. High levels of both specific and total immunoglobulin E can be a predictive marker of the possibility of fungal allergy symptoms. This information should be taken into account for the diagnosis and prevention of fungal allergy and other diseases caused by fungi as well as for allergy forecast.

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The authors have declared they have no competing interests.

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