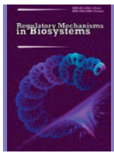

Regulatory Mechanisms
in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.

Persistence of *Candida* spp. in patients with inflammatory diseases of the respiratory and gastrointestinal tracts: analysis of laboratory studies in Kharkiv Region, Ukraine (2019–2021)

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Article info
Received 10.03.2025
Received in revised form 12.04.2025
Accepted 04.05.2025

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Bolshakova, H. M., Minukhin, V. V., Zhuravlova, I. V., Golubka, O. V., Chastii, T. V., Kuchma, I. Y., Savinova, T. V., & Shevchenko, Y. V. (2025). Persistence of Candida spp. in patients with inflammatory diseases of the respiratory and gastrointestinal tracts: analysis of laboratory studies in Kharkiv Region, Ukraine (2019–2021). Regulatory Mechanisms in Biosystems, 16(2), e25068. doi:10.15421/0225068

Invasive mycoses are becoming an increasingly serious threat in healthcare due to their continuous spread, the ability of pathogens to develop resistance to antifungal drugs, and the limited availability of new effective therapeutic agents for the treatment of fungal infections. Today, the most common causative agents of systemic mycoses remain fungi of the genus *Candida*, specifically *C. albicans*. Over the past decades, the epidemiological picture of candidiasis has gradually changed due to the increasing prevalence of *C. glabrata* and *C. parapsilosis* in mycotic pathology. The authors investigated the prevalence and species spectrum of *Candida* spp. as potential causative agents of candidiasis among subjects with inflammatory conditions of the respiratory and gastrointestinal tracts in Kharkiv region (Ukraine) during the period 2019–2021. The obtained results indicate a rising persistence of *Candida* spp. in the observed groups, increasing from 4.3% in 2019 and 4.7% in 2020 to 8.3% in 2021, with *C. albicans* identified as the predominant species, accounting for 82.8% of cases. Among the non-*albicans* group, *C. krusei* predominated (6.9%), while other *Candida* species were isolated significantly less frequently: *C. glabrata*, *C. tropicalis*, and *C. kefyr* were found in 4.3%, 3.4%, and 2.6% of cases, respectively. The susceptibility profile of isolated strains to itraconazole, fluconazole, and voriconazole was examined. *Candida* non-*albicans* strains exhibited increased resistance to itraconazole (42.8%) and voriconazole (57.2%), whereas *C. albicans* isolates demonstrated higher levels of fluconazole resistance (69.4%). The analysis of the obtained results suggests a further increase in infectious complications caused by fungi of the genus *Candida* among patients with inflammatory processes of the respiratory and gastrointestinal tracts, which may require mandatory laboratory control of mycotic infections and adjustments in therapeutic treatment to prevent invasive candidiasis.

Keywords: *Candida albicans*; *Candida* non-*albicans*; invasive candidiasis; inflammatory conditions; intestinal dysbiosis; respiratory tract.

Introduction

In recent years, experts from the World Health Organization and scientists have emphasized the increasing role of fungi as etiological factors of diseases, the geographical range and prevalence of which are constantly growing (Froidefond et al., 2023). The list of species associated with invasive mycoses is constantly expanding, both due to improvements in laboratory research methods and species identification of fungi from clinical samples, and due to the increase in the global population of people with reduced immune system reactivity (Díaz-García et al., 2023). Fungi of the genus *Candida*, representatives of the commensal mycobiota, have the greatest clinical significance among the causative agents of mycoses, increasingly causing nosocomial infections in Europe and America (Jackson et al., 2023; Kakde et al., 2023). The main etiological agents of candidal infection, including fungemia, are *C. albicans*, *C. tropicalis*, *C. glabrata* (according to recent changes in fungal nomenclature – *Nakaseomyces glabratus*), *C. parapsilosis*, *C. kefyr* (now *Kluyveromyces marxianus*), *C. krusei* (now *Pichia kudriavzevii*), *C. guilliermondii* (now *Meyerozyma guilliermondii*), and *C. lusitaniae* (now *Clavispora lusitaniae*) (Erami et al., 2023; Kidd et al., 2023). Less common are *C. catenulata*, *C. inconspicua*, *C. pelliculosa*, *C. zeylanoides*, *C. ciferrii*, *C. lambica*, *C. rugosa* (now *Diutina rugosa*), *C. famata*, *C. lipolytica*, *C. utilis* (Arendrup et al., 2023).

It is believed that *C. albicans* is responsible for 80–90% of all infections of this genesis, but in recent decades the epidemiology of candidiasis has been gradually changing (Mesquida et al., 2023). According to European population publications, the share of *C. albicans* as the leading causative agent has decreased from 80% to 60%, while representatives of the non-*albicans* (NAL) group, namely *C. kefyr* (10–40%), *C. tropicalis* (10–30%), *C. krusei* (*P. kudriavzevii*) (10–35%), and *C. glabrata* (*N. glabratus*) (5–40%) are increasingly isolated from patients with candidal infection (Beardsley et al., 2024). The geographical distribution of candidiasis causative agents is also changing: the share of *C. glabrata* (*N. glabratus*) has increased in Northern Europe, the USA, and Australia, and *C. parapsilosis* – in Southern Europe, China, and Latin America (Wang et al., 2024).

Of particular concern to the medical community is the spread of a new species of *Candida* – *C. auris*, the rapid spread of which is facilitated by numerous exogenous and endogenous factors (Lone et al., 2019). Most strains of *C. auris* possess multidrug resistance to known antifungal drugs, which reduces therapeutic success and increases the risk of mortality in infected patients (Plachouras et al., 2020; Kohlenberg et al., 2022).

The pathogenic properties of *Candida* are variable, depending on the species, degree of immunocompromise, and imbalance of the human microbiocenosis (Tóth et al., 2019).

The human microbiota, especially the intestinal microbiota, is an active participant in various physiological processes, including immune ones, therefore the consequences of disruption of the functional balance of the microbial composition can have a number of systemic effects including metabolic disorders, neuroendocrine changes, initiation of a cascade of inflammatory reactions, and an increased risk of chronic diseases (Zhao et al., 2023). It is known that various environmental factors such as physical, chemical, radioactive factors, as well as lifestyle and nutrition, can potentiate microecological changes (Mogilnicka et al., 2019). Dysbiotic conditions manifest as a decrease in the main resident normobiota and an increase in opportunistic commensals, including *Candida* spp. (Arastehfar et al., 2022). Thus, a favorable environment is created in which opportunistic microorganisms are able to exhibit pathogenic properties and migrate to ecosystems uncharacteristic for them, causing invasive pathology with diverse clinical symptoms (Kurilovich & Geva-Zatorsky, 2025). In addition, the risk of developing candidal infection increases in patients who are hospitalized for a long time, are on mechanical ventilation, have an immunosuppressive state against the background of oncological, endocrine diseases, viral infections, intensive therapy with antibacterial and corticosteroid drugs, chemotherapy, etc.; and in patients with chronic diseases of the genitourinary system and gastrointestinal tract (Ning et al., 2023).

Since *Candida* spp. most often colonize the intestines, genitourinary system, and skin, candidal infections of the mucous membranes, particularly the oropharynx, digestive system, and vagina, demonstrate the highest prevalence (Zeise et al., 2024). Some representatives of the commensal intestinal microbiota are capable of active colonization due to their translocation potential (Jackson et al., 2023). This was demonstrated using the example of *C. albicans*: scientists proved the identity of strains isolated from the blood of patients with candidemia to strains isolated from the rectum of the same patients (Zhai et al., 2020). The results of this scientific study confirm the hypothesis about the possibility of hematogenous spread of intestinal strains of *C. albicans* with a potential risk of developing systemic candidiasis; representatives of the NAL-group are most likely of exogenous origin (Kovalenko et al., 2020). Excessive growth of *Candida* spp. can provoke exacerbation of inflammatory processes, while existing inflammation, in turn, promotes further colonization by fungi (Kirchner et al., 2019; Marfil-Sánchez et al., 2021). This correlation between colonization by *Candida* spp. and the development of inflammatory diseases of the intestine and respiratory tract is demonstrated by the results of many experimental and clinical studies (Kusakabe et al., 2023; Zeise et al., 2024). The mechanism of this connection lies in the ability of *Candida* spp. to potentiate inflammatory processes in the body by inducing the production of various pro-inflammatory mediators, including cytokines IL-17 and IL-23, which indicate an existing risk factor for the progression of the underlying disease and disruption of reparative processes (Bacher et al., 2019; Mesquida et al., 2023). All of the above emphasizes the need to ensure proper laboratory control for the detection of *Candida*, which can be an indicator of the state of the microbiocenosis, and consequently, the human immune system.

The aim of our study was to investigate the species structure of clinically significant isolates of *Candida* spp. circulating among patients with somatic diseases – residents of Kharkiv and Kharkiv region (Ukraine). Particular attention was paid to the analysis of the prevalence of *C. albicans* and representatives of the non-*albicans* group in patients with inflammatory processes of the respiratory tract and gastrointestinal tract as potential etiological agents of candidal infection and the study of their susceptibility profile to major antifungal drugs.

Materials and methods

Written informed consent from patients was not required as the study did not include personalized data, photos, or video recordings of patients. All methods and procedures were performed in accordance with approved ethical standards and instructions.

This work was carried out at the clinical base of the Department of Clinical Immunology and Microbiology of the Kharkiv Medical Academy of Postgraduate Education (Kharkiv, Ukraine) from January 2019 to December 2021. During this period, a microbiological examination of clinical material from 1775 subjects of different age categories was conducted, who were divided into two groups: group I included individuals with inflammatory diseases of the respiratory tract (pharyngitis, laryngitis, tracheitis, bronchitis) (n = 1150); group II included individuals with clinical manifestations of colonic dysbiosis (n = 625). In group I patients, samples from the oropharyngeal mucosa and sputum were collected for laboratory examination; in group II individuals – fecal specimens.

Laboratory mycological diagnostics included: material collection, microscopy, culture examination, isolation of pure culture and identification of fungi, as well as quantitative determination of the degree of contamination of the studied samples. Native clinical material was used without prior enrichment. Primary inoculation of the obtained samples for the cultivation of *Candida* spp. was performed on solid differential diagnostic media: Sabouraud dextrose agar with chloramphenicol and gentamicin (Condalab, Spain), chromogenic agar M1297 for fungi of the genus *Candida* spp. (HiMedia, India). Isolates of *C. albicans* and *Candida* non-*albicans* with a quantitative indicator exceeding 10,000 colony-forming units per milliliter of the studied material ($\geq 10^4$ CFU/mL) were selected for further study, as this level of colonization is considered clinically relevant for the development of an infectious process. The study of the phenotypic properties of the isolated strains was carried out using a generally accepted methodology using liquid and solid cultural, differential-diagnostic, and selective media. Detection of chlamydospores and the nature of pseudomycelium growth were studied after culturing a daily culture of *Candida* spp. on rice agar (according to Elinov). To study the ability to form germ tubes characteristic of the species *C. albicans* (a non-strictly specific morphological feature), 0.1% Sabouraud medium (Pharmactive, Ukraine) with the addition of bovine serum (Biosera, France) was used. On chromogenic medium, considering its selective qualities by the color of the formed pigment, the species *C. albicans*, *C. krusei*, *C. tropicalis*, *C. glabrata* were determined. Final species identification was performed using the YST strip card for the Vitek2 Compact system (bioMérieux, Marcy l'Etoile, France, 2018). The susceptibility of the isolated *Candida* spp. isolates to antifungal drugs was determined by an automated method on the Vitek2 Compact microbiological analyzer (bioMérieux, Marcy l'Etoile, France, 2018), using AST-YS 01 cards for the following antifungals: fluconazole, itraconazole, voriconazole.

Pearson's chi-square test (χ^2) was used for statistical analysis of the results to determine the presence of a statistically significant relationship between the year of study and the presence/absence of clinically significant isolates of *Candida* spp. The value $P < 0.05$ was considered statistically significant for all studies.

Results

During the observation period, 1775 clinical samples (oropharyngeal mucus, sputum, and feces) from patients with inflammatory processes of the respiratory tract and intestinal dysbiosis were examined, among which the overall frequency of isolated clinically significant *Candida* spp. was 6.5% (116/1775). A gradual increase in the overall frequency of detection of yeast-like fungi was established in both study groups: from 4.5% (24/526) in 2019, to 5.4% (33/614) in 2020, and 9.3% (59/635) in 2021 against the background of an increase in the number of studies. The largest increase occurred in 2021, when the number of *Candida* spp. detections reached its maximum, confirming the trend towards increased colonization by opportunistic yeasts of various ecological niches of the human body.

Persistence of Candida spp. in patients with respiratory tract infection (group I). In group I, which included patients with inflammatory processes of the respiratory tract, the overall frequency of detection of yeast-like fungi was 5.9% (68/1150) of the total number of samples studied. The results demonstrate a significant increase in the frequency of isolation of *Candida* spp. during the observation period: 4.3% (14/326) in 2019, in 2020 this indicator was 4.7% (19/404), and in 2021 it reached 8.3% (35/420), which may indicate an increasing role of yeast mycobiota in the pathology of the upper respiratory tract. Detailed distribution of isolated *Candida* showed a prevalence of strains isolated from oropharyngeal mucus samples (52/68, 4.5%) compared to sputum (16/68, 1.4%), demonstrating the dominant persistence of yeast fungi in the upper respiratory tract, namely in the oropharynx, among the studied patient group.

Persistence of Candida spp. in patients with intestinal dysbiosis (group II). From group II individuals, 625 fecal samples were examined, from which 48 strains of *Candida* spp. were isolated (7.6%). The difference in the frequency of strain isolation between 2019 and 2020 was small – 5% (10/200) versus 6.7% (14/210) respectively, whereas in 2021 a noticeable increase in the level of *Candida*-positive fecal samples to 11.2 % (24/215) was recorded.

The dynamics of the overall frequency of isolation of clinically significant *Candida* spp. isolates from oropharyngeal mucus, sputum, and feces in patients with inflammatory processes of the respiratory tract (group I) and with dysbiotic disorders of the large intestine (group II) over a three-year observation period is shown in Figure 1.

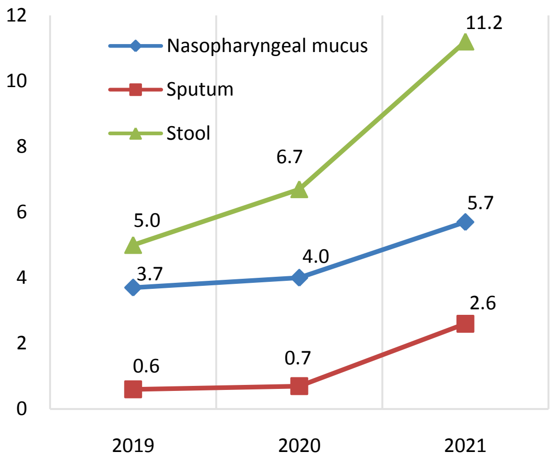

Fig. 1. Dynamics of detection of *Candida* spp. isolates in two patient groups during 2019–2021 (n = 116): the data are statistically significant (P < 0.05), indicating a reliable increase in the level of colonization by yeast-like fungi during the observation period

Within the framework of the study, species identification of 116 clinically significant *Candida* spp. isolates, obtained from the biological material of patients of group I (with inflammatory diseases of the respiratory tract, n = 68) and group II (with dysbiotic disorders of the large intestine, n = 48) was carried out. *C. albicans* remained the leading etiological agent among all isolated species during the study period – 82.8% of cases (96/116).

Significant species diversity was observed among the isolates obtained from oropharyngeal mucus. Most of the isolated strains turned out to be *C. albicans* (32/52, 61.5%), while 38.5% (20/52) of the isolates belonged to the NAL-group, within which *C. krusei* predominated (15.4%) compared to other identified species, namely *C. glabrata*, *C. tropicalis*, *C. kefyr* – 9.6%, 7.7%, 5.8% respectively, as shown in Table 1.

In contrast to oropharyngeal mucus samples, only *C. albicans* isolates (100% of cases) were detected in feces (n = 48) and sputum (n = 16).

Clinically significant *Candida* spp. isolates were tested for susceptibility to the following antifungal agents: fluconazole, itraconazole, and voriconazole by an automatic method on a Vitek 2 Compact microbiological analyzer (BioMérieux, France), using AST-YS 01 cards.

The susceptibility profile of the isolated strains to antifungal drugs, isolated from patients of both groups during the observation period, is presented in Table 2.

Table 1
Species distribution of *Candida* spp. isolates
among two clinical groups of patients (2019–2021)

Candida species	Clinical specimens							
	oropharyngeal mucus		sputum		stool		total	
	n	%	n	%	n	%	n	%
C. albicans	32	61.5	16	100	48	100	96	82.8
C. krusei	8	15.4	–				8	6.9
C. glabrata	5	9.6	–				5	4.3
C. tropicalis	4	7.7	–				4	3.4
C. kefir	3	5.8	–				3	2.6
Total	52	100	16	100	48	100	116	100

Note: isolation frequency rates are given in % with the indicated number of positive cases out of the total number of studies; n – number of isolated *Candida* spp. isolates.

Table 2
Antifungal susceptibility profile of *Candida* spp. isolated
from patients with respiratory tract inflammatory conditions
and intestinal dysbiosis (2019–2021)

Antifungal agent	Overall susceptibility profile *Candida spp.* (%, n = 116)			Susceptibility profile *C. albicans* (%, n = 96)			Susceptibility profile *NAL* (%, n = 20)		
	S	I	R	S	I	R	S	I	R
Itraconazole	57.9	10.4	31.7	58.2	13.9	27.9	57.2	0	42.8
Fluconazole	69.9	4.9	25.2	69.4	1.7	28.9	71.4	14.3	14.3
Voriconazole	65.3	2.6	32.1	72.7	3.5	23.8	42.8	–	57.2

Note: S – susceptible; I – susceptible with increased dosing exposure; R – resistant.

Analyzing the susceptibility profile of the isolated strains of yeast-like fungi over the three-year observation period, it was found that the susceptibility of *C. albicans* and NAL to itraconazole was 58.2% and 57.2% respectively, demonstrating almost complete correspondence between the studied groups (correlation coefficient 1; $P < 0.05$). A tendency towards a decrease in the level of susceptibility of *C. albicans* (69.4%) to fluconazole compared to representatives of the NAL group (71.4%) by 2% was established (correlation coefficient –1, $P < 0.05$). At the same time, the isolated strains of *C. albicans* showed higher susceptibility to voriconazole compared to isolates of the NAL group: 72.7% versus 42.8% respectively (correlation coefficient 1, $P < 0.05$).

NAL group strains demonstrated a higher level of resistance to itraconazole compared to *C. albicans* (42.8% versus 27.9% respectively; correlation coefficient 1, $P < 0.05$). At the same time, a tendency towards an increase in the level of fluconazole resistance in *C. albicans* by 14.6% compared to the NAL group was established – 28.9% versus 14.3% respectively (correlation coefficient 1; $P < 0.05$). A decrease in the level of resistance to voriconazole in *C. albicans* (23.8%) by 33.4% compared to NAL (57.2%) was also recorded (correlation coefficient –1, $P < 0.05$).

Discussion

Today, in the context of opportunistic mycoses, *Candida* spp. still remain the dominant etiological factor (Mesquida et al., 2023). Fungi of this genus belong to the group of ascomycetous yeasts, which under favorable conditions can lose their commensal nature and become the cause of both superficial lesions and severe invasive candidiasis (Tóth et al., 2019; Kidd et al., 2023). Particular attention is drawn to the increasing frequency of isolation of *Candida* non-*albicans* species, which often demonstrate higher resistance to major antifungal drugs compared to *C. albicans* (Lamoth et al., 2022).

The results of our study demonstrated the persistence of *Candida* spp. in patients with inflammatory diseases of the respiratory tract and dysbiotic changes in the large intestine. Taking into account the ability of *Candida* to translocate across epithelial barriers and potentially trigger systemic invasions under conditions of immune dysfunction, the detection of yeast-like fungi in 6.5% of cases (116/1775) among the studied patient cohorts emphasizes their clinical significance as potential pathogens. Analysis of the study results over a three-year observation period demonstrates a trend towards an increase in the number of isolated *Candida* spp. isolates in the examined individuals of both groups, with the highest frequency of detection in patients with dysbiotic intestinal disorders (group II individuals). During 2019–2020, the frequency of isolation of *Candida* spp. from clinical material of group II individuals was relatively stable with minor fluctuations (5.0% and 6.7% respectively), whereas in 2021 a significant increase in the proportion of positive samples to 11.2% was observed. Such results may indicate not only a higher overall frequency of *Candida* carriage in the intestine compared to the respiratory tract, but also an increase in colonization by fungi against the background of dysbiotic disorders in individuals of this group, possibly due to the action of exogenous factors that occurred in 2020–2021 (e.g., massive antibacterial therapy due to the SARS-CoV-2 pandemic).

Among the isolated strains, *C. albicans* was encountered most often – 82.8% of cases (96/116), which corresponds to the general global trend of dominance of this species in the etiological structure of candidal infection (Patnaik et al., 2024). This species was identified in 100% of cases from sputum and fecal samples, unlike the results of the study of oropharyngeal mucus samples, where besides *C. albicans* (32/52, 61.5%), representatives of the NAL group were detected (20/52, 38.5%). Among the strains of this group, *C. krusei* (15.4%), *C. glabrata* (9.6%), *C. tropicalis* (7.7%), *C. kefir* (5.8%) were identified, which indicates the diversity of the mycobiota of the genus *Candida* in this ecological niche and is consistent with data from scientific sources regarding the growing clinical significance of NAL species in the development of candidal infections (Mesquida et al., 2023). The obtained results indicate the need for species determination of *Candida* spp. isolates in clinical practice to optimize antifungal therapy, considering the potential differences in the natural resistance of different species to antifungal drugs.

It should be noted that from the sputum of 11 patients (2.6% of group I individuals) examined in 2021, *C. albicans* of a high concentration degree (10^5–10^7 CFU/mL) was isolated, which corresponded to 68% (11/16) of the total number of isolates of this species for the entire observation period. These patients had a history of complaints of prolonged cough for 4–5 months as a result of a previous coronavirus infection, which may indicate a link between fungal infection and post-COVID syndrome. These observations correspond to published data, showing that the development of immunopathology in severe COVID-19 may be partly due to the influence of the gastrointestinal tract mycobiota (Kusakabe et al., 2023).

The results of susceptibility testing of clinical strains of *C. albicans* and NAL-isolates over a three-year period showed almost identical susceptibility to itraconazole (58.2% vs 57.2% respectively). In terms of susceptibility to fluconazole, a slight predominance of the NAL-group (71.4%) over *C. albicans* (69.4%) was noted. At the same time, *C. albicans* demonstrated significantly higher susceptibility to voriconazole (72.7%) compared to isolates of the NAL-group (42.8%). The level of resistance to itraconazole was higher among NAL-strains (42.8%) compared to *C. albicans* (27.9%). At the same time, resistance to fluconazole in *C. albicans* reached 28.9%, which is 14.6% higher than in NAL (14.3%). Conversely, the level of resistance to voriconazole was lower in *C. albicans* (23.8%) compared to NAL (57.2%) by 33.4%. Analyzing the above data, trends of increasing antifungal resistance among the identified isolates of *C. albicans* and the *Candida* NAL-group were revealed. The high level of resistance to fluconazole among *C. albicans* (28.9%) and voriconazole among NAL-isolates (57.2%) indicates limitations in the effectiveness of basic azole drugs, which are traditionally used as the first line of therapy for candidiasis. The results of our study are consistent with data from modern scientific literature, which notes a growing trend towards resistance formation among clinical isolates of *Candida* spp.. Specifically, the decrease in susceptibility of *C. albicans* to fluconazole, established in our study (69.4%), corresponds to global observations, according to which the level of resistance to fluconazole reaches 20–30% in different regions (Routsi et al., 2022; Paiva & Pereira, 2023). The high resistance of NAL group isolates to voriconazole (57.2%) also correlates with the results of international studies demonstrating similar or even higher frequency of resistance among species such as *C. glabrata* and *C. krusei* (Arendrup et al., 2023). These data emphasize the importance of regular monitoring of the susceptibility profile of fungi to antifungals to ensure effective management of patients with candidal infections and prevent the development of resistance.

Conclusion

The results of our three-year study demonstrated an increase in the frequency of isolation of clinically significant fungi of the genus *Candida* among the examined patients with inflammatory diseases of the respiratory tract and dysbiotic disorders of the large intestine, which may indicate an imbalance of the resident microbiota and changes in the composition of the intestinal mycobiome. The prevalence of *C. albicans* (82.8%) among the isolated isolates confirms its key role in candidal infections and allows us to assert that this species continues to dominate the landscape of all other representatives of the genus. Overall, the study results underscore the clinical significance of the persistence of *Candida* spp. in the pathogenesis of inflammatory diseases of the respiratory and gastrointestinal tracts, which is associated with an increased risk of developing invasive candidiasis, especially among immunocompromised patients. The processes of fungal resistance formation to antifungal agents and their potential impact on inflammatory processes require further research. An important direction is the development of new antifungal strategies, monitoring of mycobiota, and understanding its role in the development of chronic inflammatory diseases. Further study of the mechanisms of interaction between *Candida* spp., and the immune system may open new therapeutic approaches for the treatment and prevention of associated diseases.

This research was conducted without any external funding.

The authors declare no conflict of interest.

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