VIA MEDICA

ORIGINAL RESEARCH

Barbara Garczewska[1], Sylwia Jarzynka[1, 3], Jan Kuś[2], Wojciech Skorupa[2], Ewa Augustynowicz-Kopeć[1]

[1]Department of Microbiology, Mycology Laboratory, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
[2]I Clinic of Lung Diseases, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
[3]Department of Microbiology, Central Clinical Hospital, Medical University of Warsaw, Poland

Fungal infection of cystic fibrosis patients — single center experience

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Abstract

Introduction: Cystic fibrosis (CF) is the most common monogenetic autosomal recessive disease in the human population. This systemic disease is characterized by changes in multiple organs, mainly in the lung tissue and digestive tract. More than 59% of CF patients become sensitized to fungal spores, mostly *Aspergillus fumigatus*. 5–15% of CF patients develop allergic bronchopulmonary aspergillosis. The aim of the study was to analyse the occurrence of yeast and filamentous fungi of the respiratory infections in CF patients and evaluation of drug resistance.

Material and methods: Between 2006 and 2014, mycological evaluation of 42 patients hospitalized at the National Institute of Tuberculosis and Lung Diseases was carried out.

Results: 217 specimens from pulmonary tract were collected from 42 patients with cystic fibrosis. 205 (68%) strains of yeast and 96 (32%) filamentous fungi strains were cultured. The most common mould strain was *A. fumigatus* — 22,2% (67 species). All isolates of filamentous fungi were in vitro 100% susceptible to itraconazole, voriconazole, posaconazole and amphotericin B.

Conclusions: *A. fumigatus* and *C. albicans* were the most common etiological agents of fungal respiratory pathogens associated with CF patients. *A. fumigatus* strains were *in vitro* 100% susceptible to azole and amphotericin B. Two strains of *C. albicans* and one strain of *C.tropicalis* were non-susceptible to azole (fluconazole, itraconazole and voriconazole). *Scedosporium apiospermum* was resistant to amphotericin B (MIC > 32 mg/l) and susceptible to voriconazole (MIC 0.094 mg/l).

Key words: cystic fibrosis, *Aspergillus fumigatus*, *Candida* spp., drug resistance

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Introduction

Cystic fibrosis (CF) is a systemic multiorgan and chronic condition, in which functional disorders concern mainly exocrine glands located mostly in the respiratory and alimentary systems. It is the most common monogenetic autosomal and recessive disease in white people. It is caused by mutations of the single CFTR gene located on the long arm of 7th chromosome that is responsible for the production of the CFTR protein (cystic fibrosis transmembrane regulator). The CFTR protein is a chloride channel that together with sodium channel maintain ion balance of epithelial cells of the exocrine glands. In case of damage or loss of the CFTR protein, secretion of chloride ions in cells is lowered or inhibited, and sodium ions are absorbed in increased quantities. The disturbed transport of electrolytes between the interior of epithelial cells and extracellular space causes increased water absorption and secretion condensation. In the respiratory system, mucociliary clearance is impaired, which induces development of infection and chronic

Address for correspondence: Barbara Garczewska, National Institute of Tuberculosis and Lung Diseases, Płocka 26, 01–138 Warsaw, tel. 22 43 12 142, b.garczewska@igichp.edu.pl
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inflammation leading to progressive lung damage (bronchiectasia, postinflammatory fibrosis, cysts and emphysematous bullas). Exacerbations in the course of chronic bronchopulmonary disease are the most frequent cause of hospitalisations, whereas respiratory failure — the most often cause of deaths of CF patients [1–5].

The main etiological factors of the respiratory system infections in CF patients are the following bacterial species: *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Burkholderia cepacia complex*, *Stenotrophomonas maltophila* and other Gram-negative bacteria and nontuberculous mycobacteria. Adult patients may be also infected with other microorganisms such as viruses (respiratory syncytial virus [RSV], adenoviruses, influenza viruses) or fungi (*Aspergillus* spp., *Candida* spp.) [1, 3, 6].

CF patients belong to the group with increasing risk of infection with filamentous fungi. It is possibly related to impaired mechanism of bronchial clearance and prolonged stay in the respiratory system of inhaled spores of *Aspergillus fumigatus* [7–9]. Mould spores get through the inhalation route and settle the mucous membrane of the upper airways and further migrate to the lungs [3].

Thick mucus in the airways is the source of nutrients and a perfect environment for propagation and development of fungal cells. It was found that during infection, fungal cells secrete many proteolytic enzymes (proteases, phosphatases), which inhibit their phagocytosis and facilitate adhesion and colonization in the airways [2, 3].

One of the causes of colonization of fungi in the respiratory system is the use of broad-spectrum antibiotics in treatment of bacterial infections. The study by Chotrimall showed that the use of tobramycin in treatment of *P. aeruginosa* encourages the colonization of filamentous fungi *A. fumigatus* [3].

Among the fungal species isolated from the airways of CF patients, the most frequent are the following: *A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus* and *A. nidulans*. It is believed that *A. fumigatus* and *A. terreus* species colonize the upper and lower airways of CF patients, causing pneumonia, sinusitis, bronchitis or allergic bronchopulmonary aspergillosis (ABPA) [1, 3].

ABPA is caused by hypersensitivity to antigens of the fungus that colonizes the airways. Differentiation between fungal infection and ABPA in CF patients is difficult due to similarity of clinical symptoms typical of the two conditions [8]. Additionally, the factors that predispose to the development of fungal infection are coexisting bacterial infections and a general poor condition of the patient [3].

Besides filamentous fungi such as *Aspergillus* spp., hyaline fungi such as *Scedosporium apiospermum* (*Pseudollescheria boydii*) and black yeast *Exophiala dermatitidis* are also isolated from the CF airways [1, 3]. Colonization and infections with *E. dermatitidis* occur considerably more frequently in the group of patients with pancreas failure [3]. The second species most frequently isolated from the CF airways (6.5–10%) is the filamentous fungus *S. apiospermum* [3]. *S. apiospermum* are oportunistic microorganisms whose spores are commonly found in the patient's environment (soil, water) [3]. It was shown that in patients whose the upper airways are colonized by *S. apiospermum*, infections with *Pseudomonas aeruginosa* are less frequent, whereas infections with *Staphylococcus* spp. are more often, including patients treated with penicillins [3].

Other mould species such as *Paecilomyces* spp., *Penicillium* spp., *Alternaria* spp. or *Cladosporium* spp. are seldom cultured from clinical material and possibly do not impact on increased manifestation of clinical symptoms of an underlying disease [1, 3].

The species of yeast-like fungi, *C. albicans*, less frequently *C. glabrata*, *C. parapsilosis*, *C. tropicalis* or *C. dubliniensis* are also isolated from the CF airways. Yeast-like fungi colonize the mucous membrans of the alimentary tract causing inflammation conditions of the oral cavity, oesophagus and genitourinary system [1, 3]. A long-term colonization with yeast-like fungi may occur after therapy with antibiotics and steroids [3].

The objective of the study was the characteristics of fungi isolated from the airways of patients with cystic fibrosis, hospitalized and treated at the National Institute of Tuberculosis and Lung Diseases (Instytut Gruźlicy i Chorób Płuc, IGiChP) between 2006–2014.

Material and methods

217 specimens were analysed (186 — sputum, 31 — bronchial washings) collected from the group of 42 CF patients treated at IGiChP during 2006–2014, in whom fungal infection was suspected.

The material collected from the patients was cultured on solid medium Sabouraud Dextrose Agar and incubated at the temperature of 28°C for 7–10 days. A direct preparation was made of each material, then it was evaluated in respect of elements typical of fungi, i.e. hyphae, pseudomycelium and blastospores (Fig. 1). The cultured

colonies of yeast-like fungi were identified to particular species using culture on chromogenic medium ChromAgar Candida (Graso) and incubated at the temperature of 37°C for 48 hours. Yeast-like fungi such as *Candida* spp.: *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei* were identified on a chromogenic medium according to the manufacturer's recommendations.

The other species of yeast-like fungi were identified using with biochemical test Api ID 32 C (bioMérieux) in accordance with the manufacturer's recommendations. The Api ID 32 C strips were read in the Api Extension device (bioMérieux). All cultured filamentous fungi were assigned to species basing on morphological characteristics of the colonies, hyphae, conidiophores and spores.

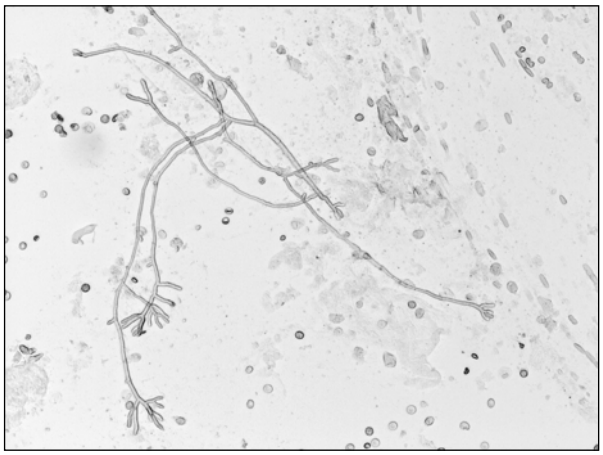

Figure 1. Hyphae *A. fumigatus* — microscopic image of a sample of sputum from patients with cystic fibrosis (× 200; collection Department of Microbiology, Micology Laboratory, Institute of Tuberculosis and Lung Diseases)

Drug-susceptibility of yeast-like fungi non-albicans to 5 — fluorocytosine (5-FC), amphotericin B (AMB), fluconazole (FCA), itraconazole (ITR) and voriconazole (VOR) was determined *in vitro* using the ATB Fungus 2 and ATB Fungus 3 strips (bioMerieux) in accordance with the manufacturer' recommendations and read in the Api Extension device. Minimal inhibitory concentration (MIC) for *A. fumigatus* strains was determined using E-test method (bioMerieux) with concentration gradient of amphotericin B (AMB), itraconazole (ITR) and voriconazole (VOR). The activity of antifungal drugs was estimated on the RPMI 1640 medium + MOPS (Biomed and bioMérieux). The interpretation of results was made basing on the recommendations of the American Clinical and Laboratory Standards Institute (CLSI) and since 2011 — in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Results

Of 217 specimens collected from the airways of 42 patients with cystic fibrosis, 205 (68%) strains of yeast-like fungi were isolated, and 96 (32%) strains of filamentous fungi (Table 1, Fig. 2). Among yeast-like fungi, 57% (171) of strains were identified as *C. albicans*, 5% (15) — *C. tropicalis* and 4.3% (13) as *C. glabrata* (Table 1). Other species of *Candida* spp. constituted 1.7% (6). Among filamemtous fungi, *A. fumigatus* species predominated — 22.2% (67) (Table 1, Fig. 1). There were also single cases of *A. niger* — 0.4% (1) and *A. flavus* — 0.4% (1). Filamentous fungi *Penicillium* spp. species (21 strains) were identified from 13

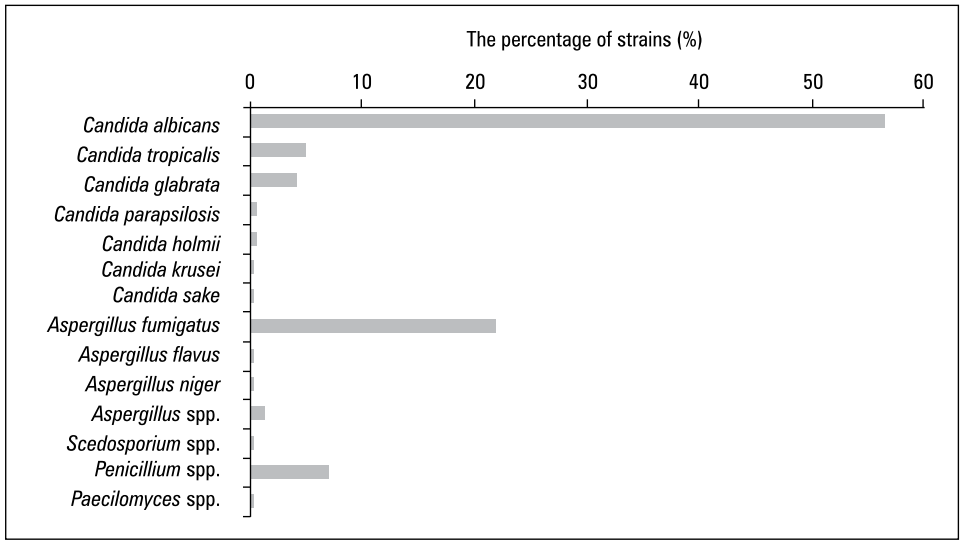

Figure 2. The percentage of fungal species isolated from patients with cystic fibrosis

patients. *Scedosporium apiospermum* was isolated from sputum of one patient (0.3%) (Table 1, Fig. 2).

Of 217 specimens, in 45% (137), yeast-like fungi strains were isolated, in 5.3% (16) strains of filamentous fungi were recovered, and in 49.2% — combined cultures (2 or 3 species) of yeast-like and filamentous fungi were found (Fig. 3). In 39 cases, 2 species of fungi were grown simultaneously: *C. albicans* and *A. fumigatus*. The pairs of the following fungi were also cultured: *C. albicans* and *Penicillium* spp. (9), *Aspergillus* spp. and *C. albicans* (4), *C. albicans* and *C. tropicalis* (3), *C. albicans* and *C. glabrata* (3) and *A. fumigatus* and *C. tropicalis* (3) (Fig. 4).

In vitro susceptibility to antifungal drugs was tested for 16 strains of filamentous fungi and 12 strains of yeast-like fungi. All 16 strains of *A. fumigatus* showed 100% of susceptibility to antifungal drugs from the azole group, i.e. itraconazole (MIC 0.25–1.0 mg/l), voriconazole (MIC 0.064–0.19 mg/l) and to a polyene drug — amphotericin B (MIC 0.19–0.38 mg/ml) (Table 3). Hyaline fungus *Scedosporium apiospermum*, which was isolated from sputum, was *in vitro* susceptible to voriconazole (MIC 0.094 mg/l) but it showed resistance to amphotericin B (MIC > 32 mg/l) and itraconazole (MIC > 32 mg/l) (Table 4). All strains of yeast-like fungi of *Candida* spp. species were susceptible to amphotericin B (100%). In the case of *C. albicans* (2 strains), resistance to azoles was observed: fluconazole (MIC 4.0 mg/l), itra-

Table 1. Species of yeast and mould isolated from pulmonary tract from patients with cystic fibrosis

Species	Number of isolates (n = 301)
Yeast	**205 (68.0)**
C. albicans	171 (57.0)
C. tropicalis	15 (5.0)
C. glabrata	13 (4.3)
C. parapsilosis	2 (0.7)
C. holmii	2 (0.7)
C. krusei	1 (0.3)
C. sake	1 (0.3)
Mould	**96 (32.0)**
Aspergillus fumigatus	67 (22.2)
Aspergillus flavus	1 (0.3)
Aspergillus niger	1 (0.3)
Aspergillus spp.	4 (1.3)
Scedosporium apiospermum	1 (0.3)
Penicillium spp.	21 (7.0)
Paecilomyces spp.	1 (0.3)

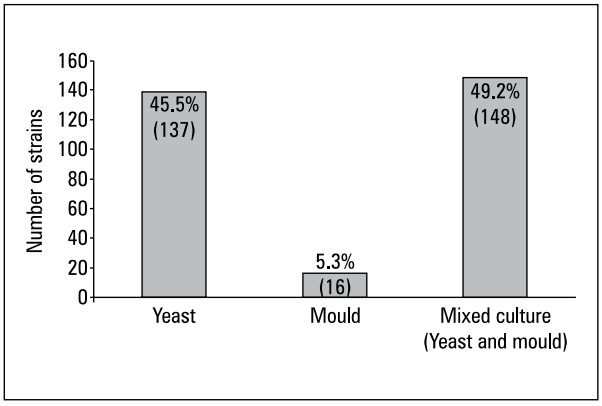

Figure 3. The number and percentage of the culture strains of yeast, mould and mixed culture from patients with cystic fibrosis

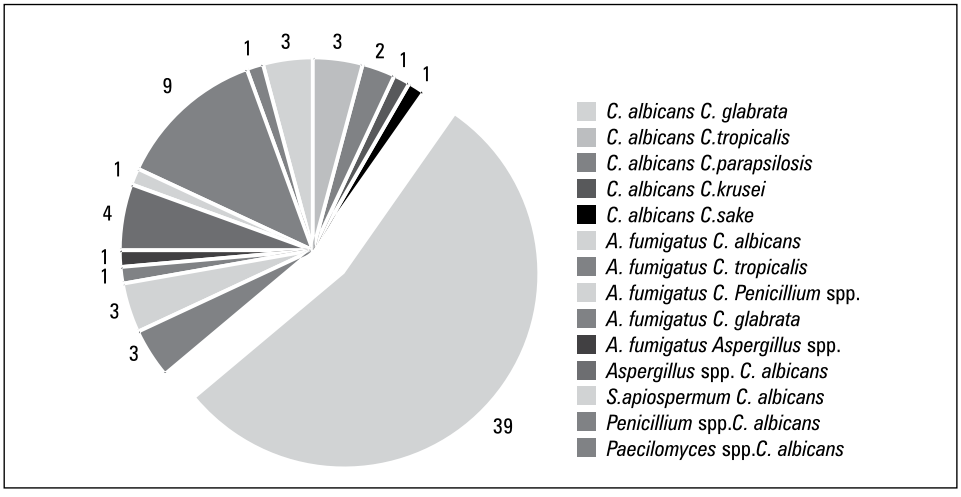

Figure 4. The pair of yeast and filamentous fungi identified from patients with cystic fibrosis

Table 2. Susceptibility to antifungal agents yeast species isolated from patients with cystic fibrosis (interpretation according to EUCAST)

Species	5FC			AMB			FCA			ITR			VOR			MYK		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
C. albicans (n = 1)	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	–
C. albicans (n = 2)	–	–	1	2	–	–	–	–	2 (MIC 4.0 mg/l)	–	–	2 (MIC 0.19 mg/l)	–	–	2 MIC 0.25 mg/l)	1	–	–
C. glabrata (n = 5)	3	–	–	5	–	–	–	4	1	1	3	1	3	–	–	–	–	–
C. tropicalis (n = 2)	–	–	–	2	–	–	1	–	1	1	–	1	1	–	1	–	–	–
C. parapsilosis (n = 1)	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	–
C. krusei (n = 1)	–	–	–	1	–	–	–	–	1	–	1	–	–	–	–	–	–	–

5FC — 5-fluorocitosine; AMB — amphotericin B; FCA — fluconazole; ITR — itraconazole; VOR — voriconazole; MYK — micafungin; MIC — minimal inhibitory concentration; S — sensitive; I — intermediate; R — resistance

Table 3. MIC50 and MIC90 for antifungal drugs against *A. fumigatus* strains (interpretation according to EUCAST)

Drug	Strains *A.fumigatus* (n = 16)	MIC50 (mg/l)	MIC90 (mg/l)	MICRange (mg/l)
ITR	16	0.38	1	0.25–1.0
VOR	16	0.125	0.19	0.064–0.19
AMB	6	0.25	0.38	0.19–0.38
POS	1	0.047	0.047	0.047

ITR — itraconazole; AMB — amphotericin B; VOR — voriconazole; POS — posaconazole; MIC — minimal inhibitory concentration

Table 4. Minimal inhibitory concentrations for antifungal drugs against *Scedosporium apiospermum* (interpretation according to EUCAST)

Scedosporium apiospermum	VOR	ITR	AMB
MIC	0.094 mg/l	> 32 mg/l	> 32 mg/l

VOR — voriconazole; ITR — itraconazole; AMB — amphotericin B; MIC — minimal inhibitory concentration

conazole (MIC 0.19 mg/l) and voriconazole (MIC 0.25 mg/l). These strains were 100% susceptible to echinocandin — micafungin (MIC 0.008 mg/l) (Table 2). One strain of *C. tropicalis* and all isolates of *C. glabrata* (5 strains) showed resistance to drugs from the azole group, i.e. fluconazole, itraconazole and voriconazole (Table 2).

Discussion

Quality and length of life of CF patients depends on the course of bronchopulmonary disease and morphological changes in the lung parenchyma. The identification of etiological factors of infection relies strongly on microbiological diagnostics. It enables proper recognition of microorganisms of the upper and lower airways, and implementation of appropriate treatment.

Among fungal species responsible for fungal infections, a prominent role assign to filamentous fungi such as *Aspergillus fumigatus*, *Scedosporium apiospermum* and *Exophiala dermatitidis* [10, 11]. Filamentous fungi are opportunistic microorganisms living in natural environment. The spores of *A. fumigatus* species nest the respiratory system of the patient and producing mycelium, which secretes protein allergens. Buarque de Almeida et al. showed the role of Asp f1, Asp f2, Asp f4 and Asp f6 proteins for the development of allergic aspergillosis in CF patients [12]. During the development of the disease high concentration of allergens in the lungs stimulates immunological response of the host. The organism of the patient produces specific antibodies, mainly immunoglobulin E (IgE) and G (IgG), whereas Th2 cells influence secretion of proinflammatory cytokines: interleukins 4, 5, 13, thus strengthening inflammatory process in the tissues [3, 13].

The present paper analysed the outcomes of microbiological tests of 42 CF patients (>18 years)

treated at IGiChP during 2006–2014. Armstead et al. in their study revealed data concerning the prevalence of cystic fibrosis in patients (>18 years) in some European countries, the USA, Australia and Canada [14]. The proportion of adult patients with CF oscillated between approximately 50% in the USA (13,657), France (2,873) and Australia (1,556), and about 60% in Canada (2,238) [14, 15]. In Poland, the only available data on the prevalence of CF > 18 years come from the Polish Cystic Fibrosis Working Group (Polska Grupa Robocza Mukowiscydozy), which reports 535 registered patients up to the end of 2012 [16].

The present study evaluated the prevalence and drug resistance of fungal pathogens in the group of CF patients treated at IGiChP in Warsaw, in whom fungal infection was clinically suspected. Mycological diagnostics of CF patients included culture of the following material: sputum, bronchial secretion, bronchoalveolar lavage. 205 strains (68%) of yeast-like fungi and 96 strains (32%) of filamentous fungi were identified. Among yeast-like fungi *C. albicans* (57%) dominated, then *C. tropicalis* (5%) and *C. glabrata* (4.3%). 1.7% constituted other species of *Candida*. Among filamentous fungi *A. fumigatus* dominated — 22.2%. Comparable proportions of yeast-like fungi were obtained by Schabereiter-Gurtner et al. In material collected from CF patients, *Candida* species constituted — 64.5%, then filamentous fungi — 35.5%, mainly *Aspergillus* species [15]. Caballero et al. also reported the prevalence of yeast-like fungi in the material collected from 35% of CF patients, and filamentous fungi isolated from 4% of patients [17].

Among the clinical material collected from the patients treated at the National Institute of Tuberculosis and Lung Diseases dominated specimens, from which one fungus species (yeast or filamentous fungus) was isolated (50%); whereas from the remaining material, two (33.3%) or three (16.7%) species of yeast-like and/or filamentous fungi were recovered (Fig. 5).

In the material from which two or three fungal species were recovered simultaneously, the most common were two species of fungi: *C. albicans* and *A. fumigatus* (13%). Corresponding results were obtained by Delhaes et al. Two fungal specimens *C. albicans* and *A. fumigatus* dominated in the material recovered from cultures of specimens from CF patients [18].

One of the most crucial pathogens responsible for fungal infections in CF patients are *Aspergillus* species. Colonization with this pathogen occurs usually after infection with *Pseudomonas* spp.

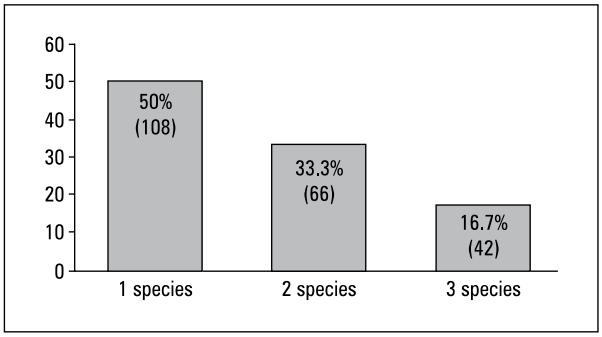

Figure 5. The number and percentage fungal species isolated from pulmonary tract from patients with cystic fibrosis

and treatment with tobramycin [3, 19]. Liu et al. tried to define indicators that distinguish colonization from infection of *Aspergillus* spp. etiology in the group of people with CF [11]. According to the authors, infection with *Aspergillus* spp. is marked by isolation of this species in > 50% of sputum specimens collected from the patient during the previous 6-12 months, worsened spirometric indices and failure of antibacterial therapy [11]. The literature reports rare cases of invasive aspergillosis in people with CF. Mortensen et al. presented two cases of invasive fungal infection of *A. fumigatus* etiology [20]. However, in the majority of CF patients, isolation of *Aspergillus* spp. only confirms colonization and/or diagnosis of allergic bronchopulmonary aspergillosis (6–25%) [20]. The Danish research showed 65.5% of colonization cases of the lower airways with *Aspergillus* spp. and 2.7% of cases of ABPA [20]. In Poland, due to lack of register of CF patients suspected ABPA, the only available data are 63 cases of suspected ABPA in CF patients > 18 years of age, which were reported in 2007 [14].

In the study, drug resistance of *A. fumigatus* strains to drugs from the azole group was tested. 100% *in vitro* susceptibility to itraconazole, voriconazole, posaconazole and amphotericin B was found. However, it should be underlined that the literature has already reported the cases of resistance of *A. fumigatus* isolated from people with CF to itraconazole (MIC > 1 mg/l), voriconazole (MIC > 4 mg/l) and posaconazole (MIC > 4 mg/l), and resistance to more than one drug from the azole group (multi-azole resistance) [21–23].

Resistance to azoles is related to the occurrence of mutation in the cyp51A gene, which is responsible for ergosterol reaction in the fungal cell [20]. Mortensen et al. showed that 4% of *A. fumigatus* strains that were isolated from the CF patients, have a lowered susceptibility to azole drugs [20]. Fischer et al. found resistance to itra-

conazole (MIC > 8mg/l) and cross resistance to the remaining drugs from the azole group such as voriconazole and posaconazole in 3.4% of *A. fumigatus* strains [24]. Burgel et al., similarly, showed a lowered susceptibility of *A. fumigatus* strains isolated from the patients > 18 years of age to itraconazole [23]. The lowest sensitivity of *A. fumigatus* to azoles was observed among the strains recovered from the patients who earlier underwent therapy with azole preparations [23–26]. The research carried out among CF patients in Germany and Denmark reported an alarming resistance of *A. fumigatus* strains to azoles (pan-azole resistance), being probably the result of the presence of typical TR46/Y121F/T289A mutations [24, 27]. The study at IGiChP showed low values of MIC of *A. fumigatus* strains for azole drugs: MIC 0.25–1.0 mg/l for itraconazole and MIC 0.064–0.19 mg/l for voriconazole. Comparable MIC values for azoles were obtained by Amorim et al. and Drago et al. [28–30]. The results of the researches presented, including the own study, suggest that resistance to azoles of *A. fumigatus* strains isolated from CF patients should be tested routinely.

In the present study, special attention has been drawn to the isolation of *Penicillium* spp. (7%), which, in the opinion of some researchers, is considered to be a new pathogen of respiratory infections in people with CF [18]. In the research by Valenza et al., filamentous fungi of *Penicillium* spp. species were isolated from 18.3% of CF patients [30]. Authors suggest that filamentous fungi such as *Penicillium* spp. may inhibit the airways of people with CF for a long time, with no signs of clinical infection [11]. Diagnosis is difficult because it needs differentiating between environmental strains of *Penicillium* spp. and similar of phenotype species: *Penicillium emersonii*, *Rasamsonia* spp. and *Acrophialophora* spp., which are described as potential pathogens that may cause progressive allergic bronchopulmonary hypersensitivity and invasive fungal infections in people with immunity deficiency [3, 31–33].

In the present study, hyaline fungus *Scedosporium apiospermum* was recovered from sputum culture of one CF patient. The literature reports single cases of isolation of this species in people with CF [23, 34]. Edelman et al. discovered significant proportions (28.6%) of *Scedosporium* spp. in the patients after lung transplantation. An increased number of *Scedosporium* spp. isolated in this group of patients is related probably to the therapy with inhaled antibiotics and steroids [35]. It was observed that *Scedosporium* spp. strains are usually isolated from CF patients together with *Aspergillus* spp., if *Pseudomonas* bacteria are not present [9]. It should be underlined that *Scedosporium* spp. was isolated from CF patients barely in few studies, which may be caused by the fact that culture and identification of the species is quite difficult. These fungi grow better on media Sabouraud Dextrose Agar with cycloheximide or dichloran rose bengal chloramphenicol [35]. Moreover, compared to other filamentous fungi, they require a longer incubation time (about 14 days) at the temperature from 28°C to 30°C. Furthermore, this species is susceptible to a small number of antifungal drugs, including voriconazole and posaconazole. In case of infection with *Scedosporium* spp., in particular in immunosuppressed patients, mortality reaches 54% [36–38]. The present study confirmed susceptibility of *Scedosporium apiospermum* strains to voriconazole (MIC 0.094 mg/l). The strain proved resistant to amphotericin B and itraconazole. The research by Biland et al. found single cases of resistance of *Scedosporium* spp. to posaconazole among the strains isolated from CF patients who earlier had been treated with azoles [37].

Drug resistance of yeast-like fungi to antifungal preparations was also analysed. *Candida* spp. strains showed 100% susceptibility to azoles, amphotericin B and micafungin. It was observed that two strains of *C. albicans* isolated from one patient with CF, according to the interpretation of the EUCAST guidelines, showed in vitro resistance to fluconazole (MIC 4.0 mg/l), itraconazole (MIC 0.19 mg/l) and voriconazole (MIC 0.25 mg/l). As it was reported in the clinical history, the patient underwent therapy with azoles in the past. In the study by Chotirmall et al., it was demonstrated that resistance of *Candida* species to antifungal drugs may be influenced by the ability of these strains to grow in biofilm structure [3].

The results of the present study and other researches prove that fungi, particularly *A. fumigatus* species are a potential pathogen of severe invasive respiratory infections in CF patients [39]. Therefore, an efficient antifungal therapy in CF patients has to be preceded with mycological examination in order to determine etiology of infection and drug-sensitivity of the pathogen to antibiotics. Currently, there is a need for developing an algorithm of mycological diagnostics of filamentous fungi, in particular the pathogens responsible for colonization and infections of CF patients [40].

Conclusions

1. In airway samples from 42 CF patients, *A. fumigatus* and *C. albicans* species dominated.
2. The evaluation of *in vitro* drug resistance of filamentous fungi showed that *A. fumigatus* were 100% susceptible to the azole drugs and amphotericin B.
3. *C. albicans* strains present resistance to the azole drugs: fluconazole, itraconazole and voriconazole.

Conflict of interest

The authors declare no conflict of interest.

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