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Original papers

Drug susceptibility of fungi isolated from ICU patients

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ABSTRACT. *Candida* species can be a reason of infections associated with high morbidity and mortality. The risk of invasive candidosis for patients admitted to intensive care units (ICUs) is increased due to immunosuppressive states, prolonged length of stay, broad-spectrum antibiotics and *Candida* colonization. The aim of the study was to determine selected properties of fungi isolated from patients treated in the ICUs of hospitals in Lodz. The materials were collected from the oral cavity, the tracheostomy or endotracheal tube and urine from 16 children and 35 adult. In total, 127 samples were examined to differentiate the fungal strains with used morphological and biochemical methods. *Candida* species were isolated from adult patients (82.9%), but were not isolated from any of the children; *C. albicans* was the predominant fungus (61.7%), much less frequent were *C. glabrata* (12.8%), *C. tropicalis* (6.4%) and *C. kefyr*, *C. dubliniensis* (4.3% each).The susceptibility of fungi to antimycotic drugs revealed that almost all of the strains were susceptible to nystatin (97.9%) and to amphotericin B (72.3%), and resistant to fluconazole (72.3%) and ketoconazole (57.5%). No isolation of fungi from children remaining in ICU may be an evidence of high sanitary regime at these wards; fungi from the genus *Candida* are the etiological factors for ICU infections; 3/5 of them are caused by *C. albicans*, mostly of the code 2 576 174, characteristic for strains isolated from hospitalized patients; it is necessary to determine the species of the fungus and its susceptibility to drugs, which allows to conduct effective therapy; prophylactic administration of fluconazole leads to an increase in the number of strains resistant to this chemotherapeutic agent; in the antifungal local treatment, nystatin should be a drug of choice as the drug to which most fungi are susceptible.

Key words: fungi, *Candida*, intensive care unit, susceptibility to drugs

Introduction

The predominant nosocomial fungal pathogens include *Candida* spp., *Aspergillus* spp., *Mucor* spp., *Rhizopus* spp., *Fusarium* spp., and other molds, including *Scedosporium* spp.

Candida species are one of the most common etiologic agents of bloodstream infection (BSI) in non-neutropenic patients admitted to intensive care units (ICU) and are responsible for 8–12% of cases. Systemic candidosis remains the fourth most common infection in the United States and the sixth up to tenth most common cause of BSI in European surveys accounting for 2–3% [1–3].

More than 200 species of *Candida* are known, but only a small number of them create clinical problems. There are at least 15 distinct *Candida* species that cause human diseases, but more than 90% of invasions are caused by the five most common pathogens: *C. albicans*, C. *glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* [4].

Invasive candidosis and candidemia are severe complications in the ICU and also important causes of morbidity and mortality (37–75%), especially in patients with severe sepsis. Factors contributing to fungal infections are, among others, hospitalization (particularly in ICU lasting for more than 21 days), the severity of the patient's condition, therapy (steroids, broad spectrum antibiotics, especially a few antibiotics at the same time or repeated rotation of antibiotics), factors impairing tissue integrity or the integrity of mucocutaneuos barriers, the extent of surgical procedures as well as colonization of more than one site or extensive colonization of one place [5].

A high proportion of ICU patients become

colonized with *Candida* species, but only 5–30% develop invasive candidosis. Progressive colonization and major abdominal surgery are well-known risk factors for *Candida* infection [6].

Taking the above under consideration, the objectives of this research were to determine selected properties of fungi isolated from patients treated in the ICUs of hospitals in Lodz and to evaluate the antifungal susceptibility profiles of identified *Candida* sp. strains.

Materials and Methods

The material was collected from 16 children (10 boys and 6 girls) between 4 days of age to 8 years ($\bar{x}$ = 3 months old) and 35 adults (23 men and 12 women) from 25 to 91 years old ($\bar{x}$ = 61.7 years old). The patients were admitted to the following hospitals in Lodz: the Polish Mother's Memorial Hospital Research Institute, the Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz – the Central Veterans' Hospital, M. Pirogow's Hospital, Copernicus Hospital and the Maria Konopnicka University Teaching Hospital.

The children remained in the intensive care unit from 2 to 120 days ($\bar{x}$ = 39 days) and were intubated for a period of 3 days to 5 months ($\bar{x}$ = 37 days).

Most of the examined children, according to ICD-10 classification, were admitted to hospital because of cardiovascular disorders originating in the perinatal period (P29), respiratory failure of newborn (P28.5), extreme immaturity (P07.2) and other preterm infants (P07.3) – 3 patients due to each cause. Other reasons for hospitalization were: streptococcal sepsis (A40), multiple congenital malformations, not elsewhere classified (Q89.7), acute upper respiratory infections of multiple and unspecified sites (J06) – 2 patients each. In individual cases the causes of hospitalization were: bacterial meningitis, unspecified (G00.9), chronic vascular disorders of intestine (K55.1), malignant neoplasm of brain (C71), respiratory failure, not elsewhere classified (J96), cerebral haemorrhage due to birth injury (P10.1), neonate respiratory distress (P22), pulmonary haemorrhage originating in the perinatal period (P26), congenital subaortic stenosis (Q24.4) and other specified congenital malformations (Q89.8).

Adults remained in the intensive care unit similarly as long as children, i.e. from 2 to 117 days ($\bar{x}$ = 17.2 days) and were intubated for a similar period of from 1 day to 4 months $\bar{x}$ = 14.5 days). On average, however, most of the children remained in the ward and were intubated for more than twice as long as adults.

Adults were admitted to hospital mostly on account of respiratory failure (J96.0) – 10 patients, cardiac arrest with successful resuscitation (I46.0) – 7 patients and superficial injuries involving multiple body regions (T00) – 5 patients. 2 patients were hospitalized due to acute pancreatitis (K85), sequelae of injuries of head (T90) and septic shock (R57.2) each. Occasional causes of hospitalization were: pneumonia, organism unspecified (J18), Guillain-Barré syndrome (G61.0), gastrointestinal haemorrhage, unspecified (K92.2), respiratory arrest (R09.2), intracerebral haemorrhage in hemisphere, subcortical (I61.0) and surgical operation with whole organ transplant (Y83.0).

Material for the study was collected from the oral cavity, the tracheostomy or endotracheal tube and urine, but also – in one case – from the peritoneal cavity. In total, 127 samples were collected. Seven children and 13 adults were at that time in the course of antifungal therapy.

The collected material was seeded directly into liquid Sabouraud medium, incubated at 37°C for 24 h. Subsequently, the cultures were left at room temperature for further 48 hours. After that, preparations from grown colonies in 0.9% solution of sodium chloride were made and microscopically examined in search for characteristic structures of fungi. If such structures were detected, the cultures were subcultured on Sabouraud agar, incubated at 37°C for 48 h and their macroscopic features were evaluated. Then the colonies were transferred to fresh media to enable the isolation of pure bacteria-free strains (axenic cultures). Morphological and biochemical methods were used to differentiate the fungal strains. The macroscopic features of the colonies (colour, shape, lustre, edges, surface, relation to agar surface, changes in colour) as well as the microscopic aspects of the microcultures were evaluated on special media [7].

Selected biochemical features of individual strains were examined by performing auxanograms with the use of API 20C AUX test (bioMérieux) which is a biochemical test of identification for precise determination of the most common fungal species. On the basis of this test, yeast-like fungi were classified into adequate genera and species based on the numerical classification described by the manufacturer (Analytical Profile Index,

bioMérieux, Lyon, 1990).

The susceptibility testing of strains to antimycotic drugs (nystatin, amphotericin B, miconazole, ketoconazole, fluconazole, itraconazole) was performed by the disc-diffusion method (BioMaxima SA). The degree of susceptibility was determined according to the manufacturer, based on the size of growth inhibition zones around the discs. Based on accepted standards, fungi may be defined as: susceptible, moderately susceptible or resistant.

Results and Discussion

In the present study, fungi were isolated from 29 out of 35 adult patients (82.9%), but were not isolated from any of the children (Table 1). Moreover, fungi were not isolated from 6 out of 13 adults that were in the course of antifungal therapy.

In contrast to our study, a number of other researchers show the presence of fungi in various specimens taken from children and neonates treated in ICU and in other wards. For example, in the research of Mahmoudabadi et al. [8] on the material taken, similarly to us, from the oral cavity swabs, urine and blood of hospitalized children aged between less than 1 week and 12 years, the authors demonstrated the presence of fungal strains in all specimens, excluding the blood. *Candida* species were isolated from 34% of swabs from the oral cavity, with *C. albicans* being the most frequent (61.5%), followed by *C. glabrata* (12.9%) and *C. tropicalis* (7.6%); other species constituted 18% in total. Moreover, from 21% of urine samples positive for fungal growth, *C. albicans* was most commonly isolated species (64%), followed by *C. glabrata* (20%), *C. tropicalis* (4%) and other *Candida* species (12% in total).

Other researchers also obtained results different than ours. They examined children between less than 1 month old up to 18 years old and found out that *Candida* sp. was an etiological factor for candidemia (50.7%), candiduria (33.6%) and other types of infections (e.g. surgical site infection). They most frequently isolated *C. albicans* (47%), followed by *C. parapsilosis* (8.2%), *C. tropicalis* (4.5%), *C. glabrata* (3.7%), *C. lusitaniae* (2.2%), *C. kefyr* (1.5%), *C. guilliermondii* (0.7%) and *C. krusei* (0.7%) [9].

Gholamipour et al. [10], also in contrast to our research, found the fungi in the material taken from hospitalized children. This team isolated 72% of *C. albicans* and 28% of other *Candida* species among 4.3% of candiduria cases in children from neonates to 15 years old and noticed that those infections occurred mostly in the patients under 5 years of age.

Finally, Mesini et al. [11] observed *Candida* infections in paediatric patients, which is not consistent with our study, although they only distinguished *C. albicans* (60%) from other *Candida* species (32%) and they did not differentiate those species. In their long term prospective study (2005–2015) the authors observed that the majority of strains were isolated from urine of patients, followed by blood and peritoneal fluid. Interesting is the fact that comparing their research to the others the overall incidence of candidemia in children was less than one half of that in adults. Those observations may explain our results, in which there were no fungi isolated from the material collected from children.

In our research, among 47 isolates from adult individuals, the most frequently found were *C. albicans* (61.7%), much less frequently *C. glabrata* (12.8%), *C. tropicalis* (6.4%), *C. kefyr*, *C. dubliniensis* (4.3% each), *C. lipolytica*, *C. krusei*,

Table 1. Examined material from children and adults and the number of positive cultures isolated from adult patients

Examined material	Children	Adults	Total	Positive cultures* No (%)
Swabs from oral cavity	13	35	48	24 (68.5)
Swabs from tracheostomy / endotracheal tube	7	33	40	8 (24.2)
Urine	3	35	38	14 (40.0)
Peritoneal fluid	0	1	1	1
Total	23	104	127	47 (45.2)

* only from adults

C. humicola, *C. parapsilosis* and *C. famata* (2.5% each). This is coherent with the prospective study conducted from 2004 to 2006 in a Belgian university hospital, in which the most frequently isolated were *C. albicans* strains (55%), followed by *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* [12].

Similar results were obtained by researchers from a teaching medical ICU in France, who in patient's blood identified in sequence: *C. albicans* (61.9%), *C. glabrata* (23.8%), *C. parapsilosis* (4.8%), *C. inconspicua* (4.8%) and *C. tropicalis* (4.8%) [13]. Likewise, a retrospective multicentre cohort study conducted by Zilberberg et al. [14] showed the highest prevalence of *C. albicans* (39.6%) candidemia, followed by *C. glabrata* (35.7%), *C. parapsilosis* (16.7%), *C. tropicalis* (6.17%), *C. lusitaniae* (1.32%), *C. dubliniensis* (0.88%), *C. krusei* (0.88%) *and C. guillermondii* (0.44%).

Also Pfaller and Diekema [15], who analized data of *Candida* infections from 1997 to 2003, noticed that *C. glabrata* is the second most frequently isolated species in the United States, following *C. albicans*. Over this period *C. albicans* were responsible for on average 66.7% of invasive candidosis cases, followed by *C. glabrata* (10.6%), *C. tropicalis* (6.58%), *C. parapsilosis* (5.92%) and *C. krusei* (2.48%). Other species isolated by us, such as *C. kefyr*, *C. famata*, *C. dubliniensis* and *C. lipolytica*, were much less frequently noted by Pfaller and Diekema and accounted for 0.4%, 0.28%, 0.06% and 0.07% of infection cases, respectively. Those authors did not notice any cases of candidosis caused by *C. humicola*.

Studies carried out in the United States (Atlanta and Baltimore), similarly to our research, showed that *C. albicans* is the most frequently isolated species (38.0%), followed by *C. glabrata* (29.0%), *C. parapsilosis* (17%), *C. tropicalis* (10%), *C. dubliniensis* (2%), *C. lusitaniae* (1%) and *C. krusei* (1%) [16,17]. Among other *Candida* species the authors observed *C. orthopsilosis*, *C. metapsilosis*, *C. guilliermondii*, *C. nivariensis*, *C. fermentati*, *C. bracarensis*, *C. catenulate*, *C. pararugosa*, *C. famata*, *C. kefyr*, *C. pelliculosa*, *C norvegensis* and *C. rugosa* that constituted less than 1% of isolates [17].

Another research summarizes the frequencies of the most common *Candida* species causing candidemia in various countries [18]. It may be seen that *C. albicans* is the major cause of infection in Iceland (60.2%), Finland (70.0%), Norway (69.8%), Denmark (60.1%), the USA (45.0%) and Spain (48.2%), followed by *C. glabrata* (14.2%, 9.0%, 13.2%, 20.55%, 21.7%, 10.7%, respectively), *C. parapsilosis* (7.3%, 5.0%, 5.8%, 3.85%, 17%, 23.95%, respectively), *C. tropicalis* (9.3%, 3.0%, 6.7%, 4.4%, 10.7%, 8.85%, respectively) and *C. krusei* (1.5%, 8.0%, 6.7%, 4.4%, 10.7%, 8.85%, respectively).

Studies conducted in a tertiary referral centre in Birmingham (United Kingdom) showed that out of 107 cases of candidemia, 46.4% were caused by *C. albicans*, 33.3% by *C. glabrata*, 21.2% by *C. parapsilosis* and 7% by other species, such as *C. tropicalis*, *C. krusei*, *C. norvegensis* and *C. lusitaniae*. *C. albicans* was also the most frequently isolated species from the blood of ICU patients [19].

All the above mentioned studies are consistent with our research, placing *C. glabrata* as the second most common *Candida* species. On the other hand, there are some studies in which *C. tropicalis* is more frequently isolated [20–22] and sometimes is even the most frequently isolated among all *Candida* species [23].

Tan et al. [20] noticed that infections caused by *C. tropicalis* are more common than those caused by *C. glabrata* in tropical countries. They isolated 27 448 strains from various specimens from patients treated in ICUs and haemato-oncology wards in Asia (China, Hong Kong, India, Singapore, Taiwan, Thailand); among them were mainly *C. albicans* (65.3%), followed by *C. tropicalis* (14.2%), *C. glabrata* (13.4%), *C. parapsilosis* (4.0%) and *C. krusei* (1.5%). Moreover, those authors quoted some data from South Korea, Japan and South America to support their findings. Furthermore, Gupta et al. [21] analyzed the medical records of 144 adult patients of the ICU in New Delhi (India) from 2006 to 2010 and found that *C. tropicalis* (33.3%) was even more frequent than *C. albicans* (29.8%). On the third position among species causing ICU-acquired candidemia the authors observed *C. glabrata* (18.1%).

By studying biochemical characteristics within species linked to the possibility of carbon assimilation from various compounds it was found that the greatest diversity was characterized by *Candida albicans* – strains of this species had 4 different codes, most of which had the code 2 576 174. Slightly lower biochemical diversity was characterized by strains of *C. tropicalis* – they had 3 codes and even smaller variety was characterized by

Table 2. Recognized species of fungi and their codes

Species	Frequency of species (%)	Code	Number of strains
C. albicans	61.7	2 576 174	19
C. glabrata	12.8	2 566 174	5
C. tropicalis	6.4	6 576 174	4
		2 776 174	1
C. dubliniensis	4.3	2 000 040	5
		2 000 000	1
		2 576 375	1
		2 556 177	1
		2 577 175	1
		6 172 134	1
		6 172 130	1
C. parapsilosis	4.3	6 756 135	1
		2 756 135	1
C. famata	2.5	6 572 773	1
C. lipolytica	2.5	6 000 104	1
C. krusei	2.5	2 000 104	1
C. kefyr	2.5	6 472 426	1
C. humicola	2.5	2 777 777	1

C. parapsilosis, *C. dubliniensis* and *C. glabrata* (Table 2).

The observations that *C. albicans* is the most differentiated and that the code 2 576 174 is the most frequent are common in our department [22,24–26]. These findings are coherent with the literature data, in which only slight differences were observed in the codes of other *Candida* species. *C. tropicalis* was characterized by the codes: 2 556 175, 2 556 375, 2 576 171, 2 576 175, 2 576 175, 2 552 174 and 6 556 175, 2 572 144, 2 536 175, 2 55 6135, *C. glabrata*: 2 000 040 and 2 000 044, *C. parapsilosis*: 6 756 177, 2 756 175, 6 756 174 and 6 752 175, *C. humicola*: 2 777 776, *C. lipolytica*: 6 000 104, *C. kefyr* : 2 442 422 [27–29].

In our research, the examination of susceptibility to drugs (Table 3) revealed that almost all of the strains were susceptible to nystatin (97.9%) and a lot of them were also susceptible to amphotericin B (72.3%). The strains exhibited intermediate susceptibility mainly to itraconazole (72.3%) and miconazole (55.3%), whereas a large percentage of *Candida* sp. was resistant to fluconazole (72.3%) and ketoconazole (57.5%). Similarly to us, Das et al. [19] noticed that all *Candida* strains were susceptible to amphotericin, but – contrary to our findings – 84% were susceptible to fluconazole and 14% were intermediately susceptible to this drug. On the other hand, other authors noted that all of the isolated *C. albicans*, *C. tropicalis* and *C. parapsilosis* strains were susceptible to fluconazole [30]. Also Cleveland et al. [16] and Lockhart et al. [17] observed that only 7.3% of species were resistant to fluconazole. Among them in Atlanta and Baltimore area 49.1% belonged to *C. glabrata*, 19.3% – *C. krusei*, 12.2% – *C. albicans*, 9.22% – *C. parapsilosis*, 9.03% – *C. tropicalis* and 1.24% – *C. dubliniensis* [16]. Those results differ from ours, in which among species resistant to fluconazole 79.4% were *C. albicans*, 14.7% *C. glabrata*, and single strains belonged to *C. krusei* and *C. tropicalis* (2.94% each). Lockhart et al. [17] also observed, in contrast to our research, that there were a lot of strains resistant to itraconazole (21.1%), among which the majority were *C. glabrata* and *C. krusei*. Furthermore, the authors noticed that almost all strains were susceptible to voriconazole and echinocandins, such as caspofungin, anidulafungin and micafungin (approximately 99.0% of isolates were susceptible to each drug).

Table 3. Susceptibility of isolated strains of fungi to drugs

Drug susceptibility	NS	AMB	ITRAC	MCL	KCA	FLU
	No (%)					
Susceptible	46 (97.9)	34 (72.3)	9 (19.3)	20 (42.6)	3 (6.3)	2 (4.2)
Moderately susceptible	0	11 (23.5)	34 (72.3)	26 (55.3)	17 (36.2)	11 (23.5)
Resistant	1 (2.1)	2 (4.2)	4 (8.4)	1 (2.1)	27 (57.5)	34 (72.3)

Explanations: NS–nystatin; AMB–amphotericin B; ITRAC–itraconazole; MCL–miconazole; KCA–ketoconazole; FLU–fluconazole

Table 4. Susceptibility to drugs depending on the *Candida* species and its code

Species	Code	Number of strains	Susceptibility to drugs					
			NS	AMB	ITRAC	MCL	KCA	FLU
C. albicans	2576174	9	S	S	MS	MS	R	R
C. albicans	2576174	2	S	S	S	MS	R	R
C. albicans	2576174	2	S	S	MS	S	R	R
C. albicans	2576174	2	S	S	MS	S	MS	R
C. albicans	2576174	2	S	S	MS	MS	MS	R
C. albicans	2576174	1	S	S	S	S	MS	MS
C. albicans	2576174	1	S	S	MS	MS	R	MS
C. albicans	2566174	5	S	S	MS	MS	R	R
C. albicans	2776174	1	S	MS	MS	MS	R	R
C. albicans	6576174	2	S	S	MS	MS	R	R
C. albicans	6576174	2	S	S	MS	MS	MS	R
C. glabrata	2000040	2	S	MS	R	S	MS	R
C. glabrata	2000040	1	S	MS	R	S	MS	MS
C. glabrata	2000040	1	S	S	MS	S	MS	R
C. glabrata	2000040	1	S	MS	R	S	MS	R
C. glabrata	2000000	1	S	S	MS	MS	R	R
C. tropicalis	2576375	1	S	S	MS	MS	R	R
C. tropicalis	2556177	1	S	MS	MS	S	MS	S
C. tropicalis	2577175	1	S	S	MS	S	R	MS
C. dubliniensis	6172134	1	S	MS	S	S	MS	MS
C. dubliniensis	6172130	1	S	MS	S	S	MS	MS
C. parapsilosis	2756135	1	S	MS	S	S	S	S
C. parapsilosis	6756135	1	S	MS	S	S	S	MS
C. famata	6572773	1	S	S	MS	S	MS	MS
C. lipolytica	6000104	1	S	R	MS	S	S	MS
C. krusei	2000104	1	R	R	S	R	R	R
C. kefyr	6472426	1	S	R	S	S	MS	MS
C. humicola	2777777	1	S	MS	MS	S	R	MS

Explanations: NS – nystatin; AMB – amphotericin B; ITRAC – itraconazole; MCL – miconazole; KCA – ketoconazole; FLU – fluconazole; S – susceptible; MS – moderately susceptible; R – resistant

After analysing susceptibility of 6 isolated *C. glabrata* strains it was found that 5 strains were resistant to fluconazole (83.3%), 4 strains were resistant to itraconazole (66.6%) and all were susceptible or moderately susceptible to other drugs used in this research (Table 4). Those results are compatible with other studies that consider *C. glabrata* as fluconazole-resistant, potentially resistant or dose-dependently sensitive [16,17,21,31–33], but are contrary to the findings of Gaspar et al. [30] who found out that all of the *C. glabrata* strains isolated in their research were sensitive to this drug. The second species commonly considered as resistant to fluconazole is *C. krusei* [16,23,32], which in our study also showed this tendency, but it has to be reminded that only one strain of this species was isolated. According to an 11-year period study [34] all *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei* strains were completely resistant or with reduced susceptibility to fluconazole but, on the other hand, Das *et al.* [19] in their research noticed 39.0% of *C. glabrata* strains of intermediate susceptibility to this agent, and only one *C. glabrata* and one *C. krusei* strain resistant to this drug.

In our research, *C. albicans* strains demonstrated wider variety of sensitivity to drugs: 100% of them were susceptible to nystatin, 96.5% were also

susceptible to amphotericin B, whereas 93.1% were resistant to fluconazole and 75.9% to ketoconazole. None of the strains was resistant to itraconazole and miconazole, but they were mostly moderately susceptible to those drugs (89.6% and 82.7%, respectively). All the results are shown in Table 4. Slightly different findings obtained Das et al. [19] who noticed that all *C. albicans* strains were susceptible to amphotericin, but also to fluconazole and itraconazole; they were also susceptible to drugs not taken into account in our studies, such as voriconazole and caspofungin. Those results are supported by other authors [23] who observed that the vast majority out of 192 *C. albicans* strains were susceptible to amphotericin B, fluconazole, itraconazole, and also to posaconazole, voriconazole, anidulafungin, caspofungin and micafungin. Moreover, the long term research of Tyczkowska-Sieron et. al. [34] exhibited that all *C. albicans* strains were susceptible to fluconazole.

According to some authors [34,35] prior use of fluconazole may be a risk factor for infections caused by *Candida* species other than *albicans*, but our results suggest that it may be applied also to *C. albicans* infections as a lot of strains were resistant to it. Tyczkowska-Sieron et. al. [34] also noted a directly proportional correlation between *C. albicans* infections and consumption of fluconazole which was used for the treatment of proven candidosis as well as for pre-emptive treatment of the suspected infections. However, the authors were not sure about the influence of fluconazole administration on the infections caused by other species of *Candida*. They did not observe a correlation between those two matters straight away, but such a correlation was noted after the assumption of a 1-year delay between the time of fluconazole use and initiation of infection. Therefore, it cannot be excluded that fluconazole therapy is a possible risk factor for development of infections caused by those fungi and there is a need for more research in this topic. On the contrary, Zilberberg et al. [14] identified more *C. albicans* strains among the patients who did not undergo fluconazole prophylaxis as compared to those who obtained such prophylaxis, but some other *Candida* species (mainly *C. glabrata*, but also *C. parapsilosis*) were more frequently isolated from the patients after fluconazole prophylaxis. Summarizing, Tyczkowska-Sieron et. al. [34] made some calculations and put forward a theory that a reduction to 0 of fluconazole use may cause 0.52 per 100 non–*C. albicans Candida* infections in 1 year as compared to almost infinite consumption of this drug, which may cause 7.3 per 100 infections in the same period. On the other hand, it must be mentioned that prophylactic administration of fluconazole and other azoles reduces the frequency of *Candida* infections and in some cases also reduces mortality [32,36–38]. Regarding the treatment of *C. glabrata* infections, often resistant to fluconazole and cross-resistant to other azoles, it is recommended to use drugs from echinocandin class, which we cannot confirm as we did not evaluate susceptibility of the isolated fungal species to this medicine [33]. Nevertheless, we certainly recommend nystatin as a drug of choice in the antifungal local treatment of candidosis caused by various species of this fungus.

Based on this research the following conclusions were drawn: 1. Fungi from the genus *Candida* are the etiological factors for ICU infections, 3/5 of them are caused by *C. albicans*, mostly of the code 2 576 174, characteristic for strains isolated from hospitalized patients; 2. It is necessary to determine the species of the fungus and its susceptibility to drugs, which allows to conduct effective therapy; 3. Prophylactic administration of fluconazole leads to an increase in the number of strains resistant to this chemotherapeutic agent; 4. In the antifungal local treatment, nystatin should be a drug of choice as the drug to which most fungi are susceptible.

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