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Distribution of fungemia agents in five years and antifungal resistance

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Abstract. – OBJECTIVE: Recent research has suggested that fungemia may demonstrate an epidemiologic shift in etiologic agents. This study focuses on the agents causing fungemia and antifungal resistance in a tertiary hospital.

PATIENTS AND METHODS: We evaluated all-age fungemia cases admitted to Balikesir Ataturk City Hospital in 2017-2021. Blood cultures (BC) were studied using BacT/Alert® 3D (bioMérieux, Marcyl'Etoile, France) and Render BC128 System (Render Biotech Co. Ltd., Shenzhen, China). On the data, we explored only the first fungal positive samples or the first isolates in different episodes of the same patients. Upon The Clinical and Laboratory Standards Institute (CLSI) disk diffusion guidelines, conventional methods and the Phoenix™ 100 System (Becton Dickinson, Franklin Lakes, NJ, USA) were utilized for antifungal susceptibility identifications.

RESULTS: The findings showed that 325 (0.84%) of 38,682 BC sets were positive for fungal growth. Except for four cases (1.2%) [*Saprochaete capitata* (n = 2); *Trichosporon asahii* (n = 1), and *Saccharomyces cerevisiae* (n = 1)], all positive cases yielded *Candida* spp. (98.8%) growth. In these patients, the following *Candida* spp. were isolated: *Candida albicans* complex (n = 155; 47.7%), *Candida parapsilosis* complex (n = 127; 39.1%), *Candida glabrata* complex (n = 19; 5.85%), *Candida tropicalis* (n = 12; 3.7%), *Candida kefyr* (n = 5; 1.54%), *Candida krusei* (n = 2; 0.62%), and *Candida guilliermondii* complex (n = 1; 0.31%). We also realized that while none of the *Candida* spp. had echinocandin resistance, 8 *C. parapsilosis* complex isolates were resistant to fluconazole, and 17 *C. parapsilosis* complex and 2 *C. tropicalis* isolates were susceptible dose-dependent to fluconazole.

CONCLUSIONS: In brief, antifungal resistance is more likely to restrict therapeutic options, albeit it is, fortunately, not prevalent in Turkey despite a few recent reports. Yet, a robust detection or management of antifungal resistance requires species-level identification and strict compliance with relevant management guidelines. Besides, challenges in research may be compensated with a national data set built with data from local laboratories.

Key Words:
Invasive fungal infections, Bloodstream infections, Fungi, *Candida*.

Introduction

Invasive fungal infections (IFIs) are often characterized by high mortality rates with a loss of nearly two million annually[1]. Although IFIs are associated with several predisposing factors (e.g., infections), there are also cases without such underlying conditions. In general, etiologic agents of IFIs are mainly predicted by geographic location, clinical status, and underlying disorders; nevertheless, the most prevalent causative agents are known to be *Candida* spp – top five causative species are *Candida albicans* complex, *Candida glabrata* complex, *Candida parapsilosis* complex, *Candida tropicalis*, and *Candida krusei*. Recently, the literature has reported an epidemiologic shift in the alignment of causatives in IFIs[1-3].

Among the deadliest IFIs, the microbiological diagnosis of fungemia mainly depends on blood culture (BC) findings[4]. In the last decade, relevant authorities [e.g., the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)] have released several guidelines in the diagnosis and management of fungemia cases[5-8]. The recommendations on these guidelines primarily hinge upon the clinical status, infection types, and molecular structures of fungi, as well as their *in vitro* susceptibility to antifungals. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and The Clinical and Laboratory Standards Institute (CLSI) have also integratively published standard procedures, epidemiological cut-off values (ECOFFs), and clinical breakpoints (CBPs) in antifungal susceptibility testing (AFST) to optimize antimicrobial therapy. Accordingly,

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species-level identification and AFST are routinely recommended in fungemia cases since proper early treatment directly affects its prognosis[9-12]. However, the reference broth microdilution (BMD) as an antimicrobial susceptibility testing method is known to be expensive and requires experienced staff to be performed. Moreover, limited data exist for only particular species and antifungals in CLSI and EUCAST standards, further restraining laboratories from leading clinicians in fungemia cases[9]. On the other hand, CLSI disk diffusion is also a reference but a more convenient testing method with a recently widened spectrum, but it is still not possible to assess any species except "Top 5[11,12]".

Epidemiologic alterations in etiologic agents and antifungal resistance (AFR) may be a hot but undermentioned issue within infectious diseases. Besides, as in bacterial infections, surveillance data of fungi is deemed essential for tracking the local/national status of fungal infections to lead to national guidelines. Thus, the present study attempted to address fungemia agents in a five-year period in a tertiary hospital and their antifungal resistance in the last two years.

Patients and Methods

Sample

We considered the findings of routine blood cultures (BCs) obtained from patients in all age groups at Balikesir Ataturk City Hospital in 2017-2021. BCs were studied using BacT/Alert® 3D (bioMérieux, Marcyl'Etoile, France) and Render BC128 System (Render Biotech Co. Ltd., Shenzhen, China). On the data, we explored only the first fungal positive samples or the first isolates in different episodes of the same patients.

Methods

All positive BC vials were Gram stained and subcultured onto 5% sheep blood agar, eosin-methylene blue agar, chocolate agar, Sabouraud dextrose agar (SDA) with chloramphenicol and gentamicin (RTA Laboratories, Kocaeli, Turkey), and ROSACHROM *Candida* Agar (Gül Biology Laboratories, Istanbul, Turkey). Plates were incubated at 35-37°C in a 5% CO_2 atmosphere for at least 48 hours. Conventional methods and the Phoenix™ 100 automated system (Becton Dickinson, Franklin Lakes, NJ, USA) with cornmeal tween 80 agar (RTA Laboratories, Kocaeli, Turkey) were utilized for antifungal susceptibility identifications.

AFST

AFSTs were applied using the disk diffusion method (Fluconazole 25 µg, Voriconazole 1 µg, Caspofungin 5 µg; Bioanalyse, Ankara, Turkey) upon the CLSI-M60 guidelines. *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258 were used for quality control purposes[11,12]. The testing could be applied for only the samples obtained within two years since previous isolates were not stockpiled, and regular AFST was not possible at the center. Any test with suspicious results was re-performed.

It should also be noted that AFSTs could not be applied for *C. glabrata* complex, *C. tropicalis*, *Candida kefyr*, *Saprochaete capitata, Trichosporon asahii,* and *Saccharomyces cerevisiae* due to lack of zone diameter breakpoints and interpretive categories of tested antifungals. While fluconazole was not tested (intrinsic resistance-IR) for *C. krusei, Candida guilliermondii* complex was only tested against caspofungin (no data on azoles). Finally, *T. asahii* was reported as IR for echinocandins. The findings were categorized as susceptible (S), intermediate (I), susceptible dose-dependent (SDD), and resistant (R).

Statistical Analysis

Since we designed the present research as a retrospective descriptive study, we share the ratios of fungemia-caused patient loss (FCPL) by services given the patient data. In addition, we statically analyzed the research data using the SPSS 22.0 (IBM Corp., Armonk, NY, USA) program. Categorical variables are denoted as numbers and percentages, and we performed a Chi-square test the compare the data between the independent groups. A p-value < 0.05 was considered statistically significant.

Results

The findings showed that 325 (0.84%) of 38.682 BC sets were positive for fungal growth. Except for four cases (1.2%) [*Saprochaete capitata*, (2), *Trichosporon asahii*, (1), and *Saccharomyces cerevisiae*, (1)], all positive cases yielded *Candida* spp. (98.8%) growth. In these patients, the following *Candida* spp. were isolated: *Candida albicans* complex (n = 155; 47.7%), *Candida parapsilosis* complex (n = 127; 39.1%), *Candida glabrata* complex (n = 19; 5.85%), *Candida tropicalis* (n = 12; 3.7%), *Candida kefyr* (n = 5; 1.54%), *Candida krusei* (n = 2; 0.62%),

and *Candida guilliermondii* complex (n = 1; 0.31%). When it comes to species distributions by service, while non-*albicans Candida* cases were significantly predominant in intensive care units (ICUs) and surgical services, the rate of *C. albicans* complex isolations was found to be significantly higher in internal medicine services ($p < 0.001$ for both; Table I).

Table II presents all AFST findings along with the FCPL rates. Accordingly, all caspofungin-tested *Candida* isolates were susceptible, while fluconazole resistance was only observed in *C. parapsilosis* complex isolates (n = 8), three of which were also categorized as I for voriconazole. Besides, 17 *C. parapsilosis* complex and 2 *C. tropicalis* isolates were SDD to fluconazole. The difference between FCPL rates of *C. albicans* complex (38.0%) and non-*albicans Candida* (45.4%) was not statistically significant ($p = 352$).

Discussion

Bloodstream infections (BSIs) are known to be severe death-causing reasons with 13-20% fatality rates. When compared to bacteremiae, fungemiae are relatively rare but may end up with mortality over 70%. Although *Candida* spp. are mostly encountered organisms, recent reports[13,14] indicate a rise of rare species too. In

Table I. Distribution of Isolated Species by Service (2017-2021).

Species/Service	ICUs[1,4]		Internal medicine services[2,4]		Surgical services[3,4]		Total	
	N	%	N	%	N	%	N	%
Candida albicans complex	129	41.13	15	4.62	6	1.85	155	47.6
Candida parapsilosis complex	113	34.77	4	1.23	10	3.1	127	39.1
Candida glabrata complex	14	4.31	1	0.31	4	1.23	19	5.84
Candida tropicalis	11	3.38	1	0.31	N		12	3.69
Candida kefyr	2	0.62	2	0.62	1	0.31	5	1.54
Candida krusei	2	0.62	N		N		2	0.62
Candida guilliermondii complex	1	0.31	N		N		1	0.31
Saprochaete capitata	1	0.31	N		1	0.31	2	0.62
Trichosporon asahii	N		1	0.31	N		1	0.31
Saccharomyces cerevisiae	N		N		1	0.31	1	0.31
Total							325	100

[1]General adult, cardiovascular, surgical, neurology, neonatal, and pediatric ICUs; [2]Including pediatrics; [3]Pediatrics and adult surgery services; [4]Non-*albicans Candida* cases were significantly predominant in ICUs and surgical services, while *C. albicans* complex dominance was obvious in internal medicine services ($p < 0.001$).

Table II. Antifungal Susceptibility Profiles (2020-2021).

Species/Antifungal	Fluconazole (n, %)		Voriconazole (n, %)		Caspofungin (n, %)		FCPL rate (%) $p = 0.352$[1]
	R	SDD	R	I	R	SDD	
Candida albicans complex	N	N	N	N	N	N	38
Candida parapsilosis complex	8 (6.3%)	17 (13.4%)	N	3 (2.4%)	N	N	41
Candida glabrata complex	NA	NA	NA	NA	NA	NA	58
Candida tropicalis	N	2 (16.7%)	N	N	N	N	83
Candida kefyr	NA	NA	NA	NA	NA	NA	20
Candida krusei	IR	IR	N	N	N	N	50
Candida guilliermondii complex	NA	NA	NA	NA	N	N	N
Saprochaete capitata	NA	NA	NA	NA	NA	NA	N
Trichosporon asahii	NA	NA	NA	NA	IR	IR	N
Saccharomyces cerevisiae	NA	NA	NA	NA	NA	NA	N

FCPL: Fungemia-Caused Patient Loss; SDD: Susceptible dose-dependent; R: Resistant; I: Intermediate; IR: Intrinsic resistance; NA: Not Applicable; N: None. [1]The difference between FCPL rates of *C. albicans* complex (38.0%) and non-*albicans Candida* (45.4%) was not statistically significant, but FCPL was higher in non-*albicans Candida* fungemia cases.

addition, the frequency alignment among *Candida* spp. is also in a change. Interestingly, the term "mixed fungemia" has recently been coined in the mycology literature, which implies the significance of culture- and species-level identification to be able to offer appropriate treatment[15].

Firstly, while a previous study[4] at our center shared 3-year epidemiologic data (2017-2019), the present study attempted to depict 5-year data of fungal BSIs (2017-2021) and AFR findings of the last two years to contribute to local preemptive and empirical therapies. Regarding our findings, *C. albicans* complex was discovered to be the most prevalent organism (n = 155; 47.7%), as expected, albeit high rates of *C. parapsilosis* complex (n = 127; 39.1%) seem alarming. Our findings overlap with the results of a longitudinal study of a Turkey-based mycology laboratory (21.5%)[3] and a nationwide study in Italy (26.2%)[16]. We also found that non-*albicans Candida* cases were significantly predominant in ICUs and surgical services, while *C. albicans* complex dominance was conspicuous in internal medicine services ($p < 0.001$ for both). On the other hand, our *C. parapsilosis* complex isolation rates were found to be higher than in other studies, which may be attributed to insufficient care of catheters since the majority of strains were isolated from ICUs and surgical services. Er et al[17] exactly reported the same issue, even with a higher rate of isolation in their ICUs, since Montagna et al[16] stated that parenteral nutrition in the ICUs may be a noteworthy risk factor for fungemia caused by non-*albicans Candida* species that exhibit a certainly higher mortality rate than *C. albicans* complex. *C. parapsilosis* complex was recently reported to be able to show resistance to fluconazole (>10%) and/or dwindling susceptibility, possibly due to clonal spreading[18,19]. In the first multicenter study[2] on AFR in fungemia agents from Turkey, overall fluconazole resistance of this organism was reported to be 7.7%. In this study, our findings revealed this rate to be 6.3%, slightly lower than previous reports, but SDD rates may offer a clue of future perspective (13.4%). We may classify the "I" category of voriconazole susceptibility (2.4%) as another notable issue, totally compatible with the mentioned report (2.1%). In their study, Er et al[17] documented significantly higher levels of AFR for both azoles, which might be because of methodological differences (i.e., utilizing the gradient strip test, non-reference method). Similarly, the literature hosts Turkish reports utilizing different methodologies and suggesting resistance rates in a wide spectrum (e.g., fluconazole R: 0-27%; voriconazole SDD: 0-2.1%)[20-23]. Nevertheless, further research may need to scrutinize high rates *C. parapsilosis* complex isolations with more "standardized" Turkish data on AFR.

FCPL rates of *C. albicans* complex (38.0%) and non-*albicans Candida* (45.4%) did not show a significant difference ($p = 0.352$; Table II). Nevertheless, while being higher in non-*albicans Candida* fungemia cases, this rate was the highest in *C. tropicalis* cases (83%). *C. tropicalis* is usually not that prevalent among fungemias, but it is particularly noteworthy that most of *C. tropicalis*-BSIs in lost patients were sourced by urinary tract (UTIs) and potentially nosocomial cases. This situation may indicate the same problem as in *C. parapsilosis* complex, and clonal spreading was also stated[24]. On the other hand, there is a paucity of data on the global AFR of *C. tropicalis*, but the rise of azole non-susceptibility (even pan-azole R) has become a concern recently[25]. Several Turkey-based studies[2,20,21] did not observe R to azoles in fungemia cases, as in our study (only two isolates were SDD to fluconazole). However, relevant guidelines should compose and recommend a more dedicated pharmacological approach, as well as potential microbiological resistance, by infection site.

It is particularly interesting that we detected rare species, such as *S. capitata, T. asahii,* and *S. cerevisiae*, as causative agents along with *C. kefyr* and *C. guilliermondii* complex. Although the ESCMID[8] published a management guideline for these rare yeasts, it is barely known of their AFR potential and therapeutic success against any antifungal agents. In their study, Alp et al[26] obviously stated that fungemia by noncommon species is often underestimated; thus, its susceptibility patterns may show variations. Besides, it is deemed crucial for a laboratory to be aware of diagnostic insufficiency of conventional and automated methods (BD Phoenix™ 100, Becton Dickinson (Becton Dickinson, Franklin Lakes, NJ, USA), and VITEK 2, bioMérieux, Marcyl'Etoile, Paris, France) since there was evidence in previous research[27-29] regarding misidentifications of uncommon species, including *Candida auris*; this may be how our study differs from the mentioned studies. Although the novel technology MALDI-TOF MS offers promising results to achieve this goal, joint and comparative us-

age of different techniques can also be rather helpful in facilities[29]. Of note, it should not be ignored that uncommon species might be the causative agent of a breakthrough infection due to their variable susceptibility patterns[30]; therefore, laboratories are recommended to inform clinicians immediately about such isolations.

Limitations

The present study has a few limitations. Since the CLSI disk diffusion method offers a rather limited spectrum of interpretation, we could not comment on particular species, including *C. glabrata* complex[11]. In addition, we could not make any further evaluations of these species (e.g., *FKS* mutation screening), which was already beyond the scope of this study. Besides, we could not categorize BSIs (e.g., catheter-associated, nosocomial, etc.) due to a lack of necessary data in our center's information management system. Lastly, it was unavailable and also beyond the scope of this study to evaluate species-based mortality considering other risk factors, underlying disorders, and clinical findings.

Conclusions

The species spectrum of fungi-caused BSIs has been widened, and AFR has become a crucial parameter in the prognosis of these BSIs. Indeed, *C. auris* has recently reminded the importance of continuous screening for fungi and fungi-caused BSIs[9]. Since the population of "immunoproblematic" individuals is growing worldwide, laboratories should evaluate and optimize their diagnostic capacities, relevant authorities should regularly update their guidelines, and further research and clinicians should be locked on such infections.

Ethics Approval

The Ethics Committee of the Faculty of Medicine, Balikesir University, granted ethical approval to our study (2021/201, dated 09.22.2021).

Conflict of Interest

The authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Authors' Contributions

Conceptualization, A.K.S.; methodology, A.K.S., A.Ç.D., T.K.A.; software, A.K.S.; investigation, A.K.S., A.Ç.D., T.K.A.; resources, A.K.S., A.Ç.D., T.K.A.; data curation, A.K.S., A.Ç.D., T.K.A.; writing—original draft preparation, A.K.S., A.Ç.D., T.K.A.; writing—review and editing, A.K.S., A.Ç.D., T.K.A.; visualization, A.Ç.D., T.K.A.; supervision, A.K.S.; project administration, A.K.S., A.Ç.D., T.K.A. All authors have read and agreed to the published version of the manuscript.

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