RESEARCH

Prevalence of Yeast Fungal Infections in Intensive Care Unit in Poland

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Abstract

Background: Nearly 2% of hospital intensive care unit patients are at risk of developing life threatening fungal infections. High mortality rates indicate that identification of disease causing organisms and choice of adequate medications are crucial in the therapeutic process.

Objectives: This paper focuses on describing the primary pathogens responsible for infections in medical intensive care units, and verifying the species-specific first-choice antimycotics.

Methods: A retrospective analysis of ICU patients' medical histories was performed. A database of mycological diagnoses, infection risk factors during hospital stay, therapy outcomes, and strain – drug suscepitbilities was created.

Results: *Candida glabrata* showed greater than 30% increase in incidence during 2007 -2010 when compared to results form years 1996 – 2000. Diabetes was most often recognized as a comorbid condition to *C. glabrata* infection. *C. krusei* was frequently present in patients with either liver or renal insufficiency. We observed marked fluconazole resistance in *C. albicans* and *C. krusei in vitro* cultures.

Conclusions: Critically ill patients with liver or renal insufficiency are prone to *C. krusei* infections. The changing epidemiology of fungal infections requires revision of commonly used first line antifungal drugs, due to the fact that most commonly occurring strains show high resistance to fluconazole. Fungal infections in diabetics admitted to the ICU lead to higher death rates and should be handled with caution.

Keywords: Yeast-like fungal infections; antifungal susceptibility; ICU mycoses

Introduction

Fungi of the *Candida* species are responsible for life-threatening, nosocomial infections in medical Intensive Care Units (ICUs) with an incidence ranging from 0.74% to 1.9% of all patients admitted [1, 2]. Mortality associated with fungal infections in patients hospitalized in ICUs reaches 67% [3]. Most common species of *Candida* fungi are *C. albicans*, followed by *C. glabrata* [2]. Known risk factors that predispose to candidiasis are: trauma, immunosuppression, prolonged hospital stay, diabetes, mechanical ventilation, urinary tract catheterization, and central venous catheterization [4]. Fungal infections in medical ICUs are highly resistant to antifungal therapy [5], thus early initiation of adequate treatment is crucial for the patients' survival.

The epidemiology of fungal infections changes over time [6]. Therefore it is important to verify the incidence of key *Candida* species every decade providing an update on epidemiology and susceptibility of strains to antifungal medications.

The aim of this study is to assess the risk factors related to fatal therapy outcome in patients infected with pathogenic fungi and describe susceptibility of specific strains to antimycotics. We also try to provide a profile of fungal infections in medical ICU setting.

Methods

Subjects and experimental protocol

Patient histories collected between 2007 and 2010 from medical ICUs with positive fungal infection were utilized in this research. All investigators had access to data and proofed their accuracy throughout this retrospective study, conducted at Poznań Regional Hospital. An algorithm describing the design of this study is illustrated in figure 1.

The database gathered information on: 1) diagnosis given by the mycology lab based on samples acquired in the medical ICU; 2) patient age and gender; 3) medical procedures that the patient underwent: urinary and central venous catheterization, mechanical ventilation, renal replacement therapy, parenteral nutrition, multiple invasive procedures, wide spectrum antibiotic therapy; 4) comorbid conditions: renal insufficiency, diabetes mellitus, acute pancreatitis, cirrhosis, adult respiratory distress syndrome (ARDS), neoplasms, HIV and cachexia.

The diagnosis of clinical samples was performed by the trained staff of the mycology department, and consisted of direct microscopic examination and species identification using Integral System Yeasts Plus, which allows for simultaneous antifungal susceptibility testing. The system uses a panel of 24 wells inoculated with a cell suspension previously incubated for 48 hours at 36°C. Growing yeast assimilated the specific sugars present in each well allowing their identification. The following antimycotics were used in antifungal susceptibility tests: 5-flucytosine, amphotericin B, miconazole, ketoconazole, itraconazole, fluconazole and caspofungin.

Formation of the study groups

We formed study groups according to the mycological diagnosis (Fig. 2) The mixed group was composed of rare species: *C. parapsilosis, C. lusitaniae, C. kefyr, C. sphaerica* and *C. lipolytica*. Age groups were formed according to patients' age: 18-39, 40-59, 60-79 and 80 years of age and above.

Statistical analyses

Incidence of chronic conditions associated with each group was calculated. Factors associated with increased mortality of ICU patients infected with fungi were described using either the Chi squared test with or without Yates' continuity correction or Fisher exact test where adequate. The data set was analyzed in R statistical software [7]. Wherever the term 'statistical significance' is used it refers to the test's p-value of <0.05. Considering the nature of this analysis there was no control sample.

Results

246 patient histories met the inclusion criteria. We examined 109 female and 137 male patient cases. 34 of those patients were infected with more than one pathogenic fungal strain. The final number of mycological diagnoses was 288. The majority of fungal infections were observed in patients between 60 - 79 years of age (see table 2. Full demography of our sample is illustrated by table 1.

The most common pathogen isolated from patients was *Candida albicans*. Three cases of *Candida* genus could not be specifically identified. Additionally, 3 non-yeast-like fungi were recognized, however we decided not to include them in the following comparison. A detailed description of the isolated species is available in table 3.

Tracheal aspirate culture – routinely performed in patients undergoing respiratory therapy allowed for the recognition of most strains, but mixed group yeast-like fungi were mainly isolated from urine (as shown in table 4).

The mixed *Candida* group patients showed the highest relative frequency of deaths, but this observation was not statistically significant. Nearly all examined patients underwent central venous catheterization, urinary tract catheterization and were parenterally nutritioned. It is worth mentioning that patients with concomitant diabetes were more frequently diagnosed with *C. glabrata* infection than any other genus ($p = 0.0012$). Patients infected with *C. krusei* were more often diagnosed with renal insufficiency ($p = 0.0156$), cirrhosis ($p = 0.0024$) and underwent renal replacement therapy than other groups ($p = 0.0487$). The results of *Candida* group comparisons are summarised in table 5.

When we investigated which procedures and conditions are linked with higher death rates, we found that renal and hepatic insufficiency were significantly more often connected with fatal therapy outcome. Also being above 80 years of age, and diabetic resulted in increased death risk compared with patients who lacked those factors. Wide spectrum antibiotic therapy during the ICU stay was linked to a lower death rate. The significance of those comparisons are summarized in table 6 and figure 3 illustrates their odds ratios.

C. albicans strains were the most resistant against antimycotics, and *C. glabrata* seemed to be susceptible to nearly all antimycotic drugs. Most of the strains were resistant to fluconazole. Treatment with Amphotericin B most often seemed to stop colony growth *in vitro*. Caspofungin was used in 15 *C. albicans* and 10 *C. glabrata* cases and showed to be effective in 92% of strains. Antimycotic drug susceptibility comparison can be seen in figure 2.

Discussion

Our data show a marked shift in *Candida* species distribution over the last 10 years. We have identified *C. albicans, C. glabrata, C. tropicalis* and *C. krusei* to be the most important pathogens. There are many reports that support the finding of *C. albicans* being the most common pathogen followed by *C. glabrata* and *C. tropicalis* [8, 9].

C. glabrata increases in numbers and is linked to diabetes

When we compared the incidence of fungal species to a previous study conducted in this very same ICU between the years of 1996-2000 [10], we noticed that although

C. albicans and *C. glabrata* were still the most frequently occuring pathogens, there was a decline in the number of *C. albicans* relative to the increase of *C. glabrata*. Trick et al. also observed this phenomenon [11]. The growing incidence of *C. glabrata* appears to depend on patient age and the prophylactic use of fluconazole [9, 12].

We observed a higher incidence of *C. glabrata* infections in patients suffering from diabetes mellitus. Such findings have also been reported by Segireddy et al. and Harris et al. [13, 14]. It is known that *C. glabrata* has lower virulence compared to *C. albicans*. This fact may explain why humans lack specific host defense mechanisms against this commensal microorganism. This fungus, once acquired, may be carried asymptomatically over a prolonged period of time. Diabetic patients have an impaired immune system; hence they are more susceptible to *C. glabrata* infections, contrary to a resistant, healthy population [11]. This observation may be further explained by the fact that *C. glabrata* is more often diagnosed in the diabetic patient population, which itself grows in number each year, with an annual increment of 24.000 cases for Poland as estimated by Shaw et al. [15].

Emergence of previously uncommon species

We observed previously uncommon species: *C. krusei* and *C. lusitaniae*. *C. krusei* along with *C. parapsillosis, C. kefyr* and *C. guilliermondii* are rarely isolated *Candida* species, though they are thought to be less virulent. The incidence of *C. krusei* has significantly increased in the last few decades [16]. Some authors try to explain this phenomenon by the fact that fluconazole prophylaxis is widely applied [9, 17, 18]. *C. krusei*, like other less common *Candida* species, are often resistant to azole antifungal drugs, thus a widespread fluconazole prophylaxis in ICU patients may be the cause for a sudden emergence of *C. krusei* strains [16]. Also *C. lusitaniae* could occur more frequently, due to the acquisition of multidrug resistance [19].

C. krusei and concomitant diseases

According to our research, there is a link between *C. krusei* infection and cirrhosis. We have shown that patients with cirrhosis were more frequent in the *C. krusei* infected group. Renal insufficiency was not significantly associated with *C. krusei* infections, but this may be due to low number of *C. krusei* infections described in this study. This finding was also observed by Choi et al. [20] and Ortega et al. [21]. A theoretical model in which *C. krusei* would predominantly infect single-organ-insufficient patients more than any other *Candida* species is not presently known. Our study describes the novel finding that there is higher incidence of *C. krusei* in the hepatic insufficiency group, yet undoubtedly more studies need to be done to support this. Choi et al. reported approximately 26% of their patients (5 out of 19) to have both *C. krusei* infecion and renal insufficiency [20]. These data are in parallel with ours.

Fatal therapy outcomes

We also have found that not only diabetes mellitus comorbidity contributed to the fatal therapy outcome, but chronic renal and hepatic insufficiency did as well. These findings are consistent with data from research regarding organ transplant recipients with candidemia [22].

Other factors, such as patient age and sex also have a strong impact on the result of treatment. We came to conclusion that male patients, as well as older patients with fungal infections had a poorer prognosis, in comparison to groups involving young and female patients. Interestingly, there is a strong link between Candida species and the patient's age. Neonates and infants are predominantly infected with *C. parapsilosis*, old patients with *C. glabrata*, while *C. albicans* is the most prominent species in young adults with a gradual decline towards older age groups [23].

Antibiotic Suscetibility Testing (AST)

One of our goals was to describe the susceptibility of species to certain antifungal drugs. We observed that *C. krusei* is resistant to fluconazole, a finding previously described in other studies. Orozco, who investigated the reason for this phenomenon, came to the conclusion that 14-α demetylase of *C. krusei* cells, which is a target enzyme for fluconazole, has 14 times lower susceptibility to inhibition by fluconazole than this very same enzyme in *C. albicans* species [24]. *C. albicans* fluconazole resistance is based on energy dependent drug efflux [25]. Sasse et al. identified the genes which may increase the fluconazole resistance in *C. albicans* exponentially: MRR1, TAC1 and UPC2 [26].

Fluconazole prophylaxis

Chalmers et al. conducted a survey in the United Kingdom in 2011 regarding empirical and specific therapy for *Candida* infection in Intensive Care Units. It turned out that fluconazole was the most commonly prescribed agent for both empirical treatment and lab-tested *Candida* infections [27]. Over the course of time fluconaloze was used as routine prophylaxis and is still a standard empirical drug for all *Candida* infections in many medical ICUs [27], thus causing the prominent reduction in it's effectiveness.

Competing interests

The authors declare that they have no competing interests.

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Figures

Tables

Figure 1 The study design Illustrates the design of this study with a infographic

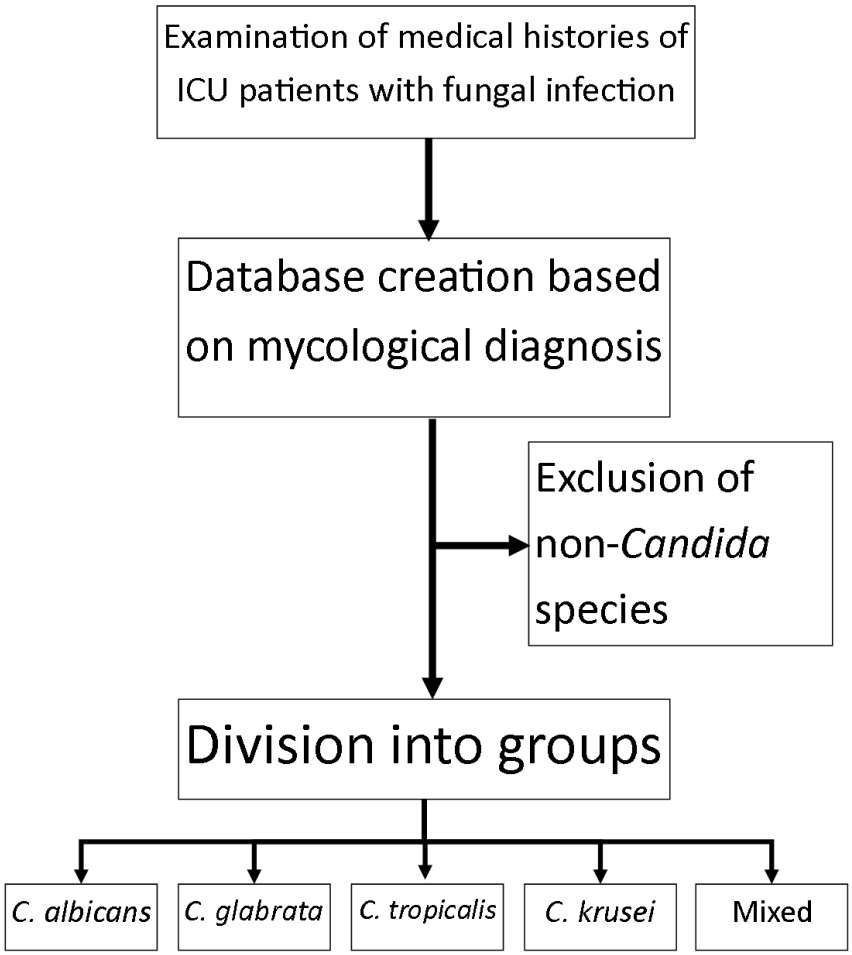

Figure 2 Candida Species susceptibility to anti-fungal drugs

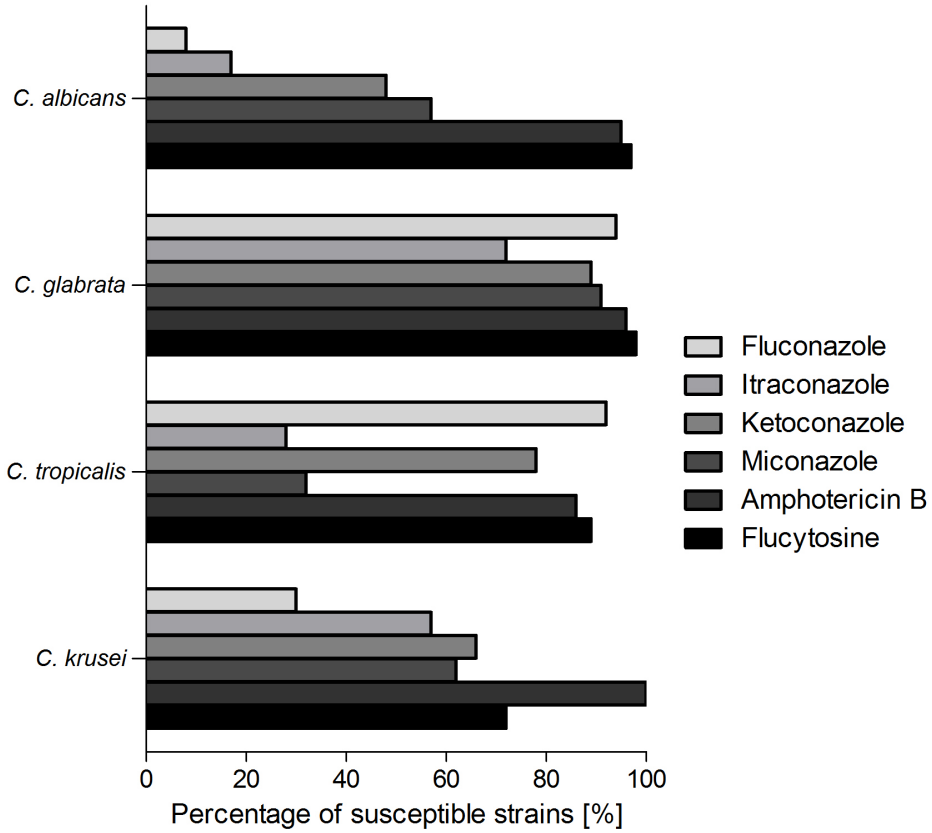

Figure 3 Odds ratios of fatal therapy outcome

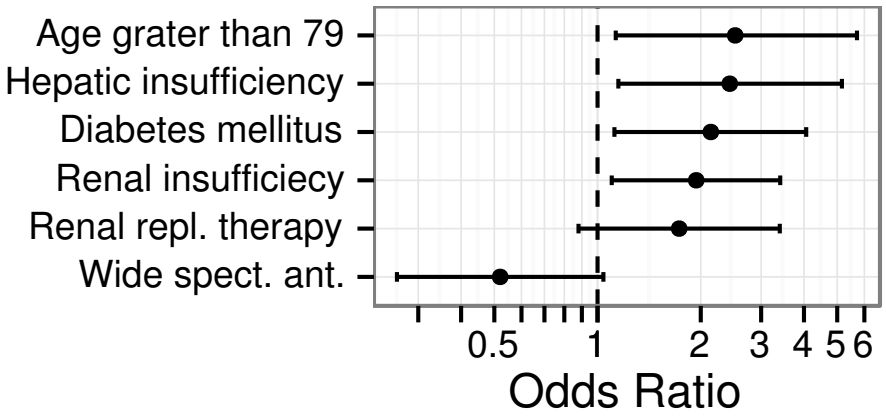

Table 1 Characteristics of 244 patients with *Candida* infection

Patient characteristics	value
Age, median (mean; range)	65 (61.2; 18-94)
Sex: male / female	135 / 109
Diagnostic category	n(%)
Medical	162 (65.85)
Surgical	41 (16.67)
Trauma	31 (12.60)
Risk factors for *Candida* infection	n (%)
Mechanical ventilation	235 (96.31)
Central venous catheeterization	220 (90.16)
Urinary tract catheterization	242 (99.18)
Previous broad spectrum antibiotic therapy	201 (82.38)
Acute kidney injury	90 (36.89)
Renal replacement therapy	51 (20.90)
Diabetes mellitus	59 (21.18)
Acute pancreatitis	14 (5.74)
Major surgery / invasive procedure	41 (16.80) / 135 (55.33)
Parenteral nutrition	216 (88.52)
Mortality, n (%)	96 (39.34)
Length of ICU stay, median, mean (in days)	12, 27

Table 2 Patient distribution among age groups.

Age group	*C. albicans* [n (%)]	*C. glabrata* [n (%)]	*C. tropicalis* [n (%)]	*C. krusei* [n (%)]	Mixed [n (%)]
18 – 39	36 (20)	4 (8)	0	0	1 (5)
40 – 59	40 (22)	14 (26)	5 (25)	5 (50)	5 (25)
60 – 79	85 (47)	28 (53)	11 (55)	4 (40)	11 (55)
80 +	21 (12)	7 (13)	4 (20)	1 (10)	3 (15)

Table 3 Pathogenic species of fungi isolated from medical ICU patients

Species	Count	Percentage
Candida albicans	182	63.19
Candida glabrata	53	18.4
Candida tropicalis	20	6.94
Candida krusei	10	3.47
Candida parapsilosis	8	2.78
Candida lusitaniae	4	1.39
Candida kefyr	3	1.04
Candida sphaerica	1	0.35
Candida lipolytica	1	0.35
Candida spp.	3	1.04
Rhodotorula glutinis	1	0.35
Trichosporon beigelii	1	0.35
Cryptococcus neoformans	1	0.35

Table 4 Site of sample collection

Material	*C. albicans* [n (%)]	*C. glabrata* [n (%)]	*C. tropicalis* [n (%)]	*C. krusei* [n (%)]	Mixed [n (%)]
Urine	34 (19)	20 (38)	4 (20)	4 (44)	11 (58)
Tracheal aspirate	123 (68)	32 (60)	16 (80)	5 (56)	5 (26)
Blood	3 (2)	0	0	0	1 (5)
Peritoneal cavity	4 (2)	0	0	0	0
Oropharyngeal cavity	16 (9)	0	0	0	1 (5)
Skin	1 (1)	1 (2)	0	0	1 (5)

Table 5 Species comparison according to factors extracted from medical history

Factor	*C. albicans* [n (%)]	*C. glabrata* [n (%)]	*C. tropicalis* [n (%)]	*C. krusei* [n (%)]	Mixed [n (%)]
Deaths	69 (38)	17 (32)	5 (25)	3 (30)	11 (55)
Medical procedures performed					
Central venous catheterization	161 (89)	49 (92)	18 (90)	7 (70)	18 (90)
Urinary catheterization	179 (98)	52 (98)	20 (100)	10 (100)	19 (95)
Mechanical ventilation	172 (95)	52 (98)	20 (100)	10 (100)	20 (100)
Renal replacement therapy	35 (19)	13 (25)	5 (25)	5 (50)	6 (30)
Parenteral nutrition	157 (86)	49 (92)	19 (95)	10 (100)	20 (100)
Multiple invasive procedures*	30 (16)	6 (11)	1 (5)	1 (10)	1 (5)
Wide spectrum antibiotic therapy#	149 (82)	47 (89)	16 (80)	10 (100)	17 (85)
Comorbid conditions					
Renal insufficiency	65 (36)	21 (40)	7 (35)	8 (80)	10 (50)
Diabetes mellitus	39 (21)	22 (42)	3 (15)	1 (10)	2 (10)
Acute pancreatitis	10 (5)	4 (8)	1 (5)	0	1 (5)
Hepatic insufficiency	29 (16)	7(13)	1 (5)	6 (60)	6 (30)
ARDS	18 (9)	6 (11)	4 (20)	2 (20)	6 (30)
Neoplasms on anamnesis	18 (10)	3 (6)	0	1 (10)	2 (10)
HIV	2 (1)	0	0	0	0
Cachexia	9 (5)	4 (8)	0	1 (10)	3 (15)
Multi-species infection	19 (11)	7 (16)	2 (13)	3 (60)	1 (9)

* Patients who underwent a minimum of two invasive procedures.
# Patients who received a minimum of two antibiotics systemically.

Table 6 Factors associated with increased death rate in patients with fungal infections

Factor	*p value*
Age above 80 years	0.012
Renal insufficiency	0.014
Diabetes mellitus	0.012
Hepatic insufficiency	0.01
Renal replacement therapy	0.084
Wide spectum antibiotic therapy*	0.044

* Patients who received a minimum of two antibiotics systemically.