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Fungal Colonization of the Respiratory Tract in Allogeneic and Autologous Hematopoietic Stem Cell Transplant Recipients: A Study of 573 Transplanted Patients

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Background: Fungal colonization and infections remain a major cause of infection morbidity and mortality following hematopoietic stem cell transplantation (HSCT) in patients with hematological malignancies. The aim of this study was to analyze the spectrum of fungal microflora of the respiratory tract (oral cavity, pharynx, epiglottis, and sputum) in patients undergoing HSCT and to evaluate the relationship between HSCT type and incidence of mycotic colonization and infections.

Material/Methods: Retrospective analysis of fungal isolates collected from the respiratory tract (oral cavity, pharynx, epiglottis, and sputum) of 573 patients undergoing HSCT was performed.

Results: The overall rate of fungal colonization in patients undergoing HSCT was 8.7%. Patients undergoing allogeneic HSCT were statistically significantly more often colonized (12.95%) compared to autologous HSCT recipients (4.7%). Colonizing cultures were mainly *C. albicans* and *C. krusei*, and sporadically *C. glabrata*, *C. famata, Aspergillus spp.* and *Saccharomyces cerevisiae*. *C. albicans* was the most frequent species found in isolates from the pharynx, sputum, and oral cavity collected from patients undergoing HSCT. Aspergillosis was more common after allogeneic than after autologous HSCT. The pharynx was the most frequently colonized site.

Conclusions: Allogeneic HSCT recipients are more susceptible to fungal infections compared to the autologous group. Selection of species during prophylaxis and antifungal therapy requires developing more effective prevention and treatment strategies based on new antifungal drugs and microbe-specific diagnoses.

MeSH Keywords: Hematopoietic Stem Cell Transplantation • Lung Diseases, Fungal • Transplantation, Autologous • Transplantation, Homologous

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Background

Patients with hematological malignancies who undergo hematopoietic stem cell transplantation (HSCT) following intensive myeloablative treatment are at risk for serious complications such as mucosal barrier injury, prolonged neutropenia, graft-versus-host disease (GvHD), and opportunistic infections [1–3]. During last 15 years, when oral mold-active azoles came into use, the rate of fungal infections has been rising [4,5]. Now, the rate of fungal infections needs to be redefined, and the rates may vary depending on access and use of mold-active antifungal agents with the transplant procedure. Fungal infections have become the leading cause of infection-related mortality after bone marrow transplantation [6]. The most frequent etiologic agents of fungal infections among patients undergoing HSCT are *Aspergillus* and *Candida* [7]. Invasive fungal infections caused by these 2 species are thought to define a population of patients with poor outcome [8].

Candida infections in patients undergoing HSCT are considered to originate from endogenous microflora in the host. Oral *Candida* colonization induces a 3-fold increase in the risk of candidemia development, and multicolonization of oropharynx and on rectal swabs is associated with significantly higher incidence of invasive infection. Mucosal barrier injury due to chemo- or radiotherapy, as well as central venous access, is very often the primary sources of candidemia [9,10].

Aspergillus infections are always exogenous. The respiratory tract is the most common portal of entry; inhalation of the spores to the nose, paranasal sinuses, and lungs may cause spreading and development of systemic disease [11].

In the present study we investigated fungal microflora of respiratory tract in patients undergoing HSCT because of hematological malignancies and the assessment of the relationship between HSCT type and incidence of mycotic colonization and infections.

Material and Methods

Retrospective analysis of fungal isolates collected from 573 patients (314 males, 259 females; mean age 44.98±14.63 years) undergoing HSCT because of hematological malignancies between 2010 and 2012 at the Department of Hematology and Bone Marrow Transplantation of Medical University of Silesia, Katowice, Poland was performed.

The study group consisted of 301 patients who underwent autologous HSCT (174 males, 127 females; mean age 50.81±12.82 years) and 272 individuals who received allogeneic HSCT (140 males, 132 females; mean age 38.53±13.42 years). The stem cells source was bone marrow, peripheral blood, or umbilical cord blood. Among allogeneic HSCT recipients, related donor (RD-BMT) was the source of stem cells in 84 cases (30.9%) and unrelated donor (URD-BMT) in 188 cases (69.1%). The characteristics of the study group are shown in Table 1.

Pre-HSCT treatment including conditioning chemotherapy with or without total body irradiation (Ida-Cyclo-TBI, Ida-Cyclo-Bus, Cyclo-TBI, or Cyclo-Bus regimen) and immunosuppressive therapy for graft-versus-host disease (GvHD) were administered. All patients received anti-infectious prophylaxis consisting of cotrimoxazole (480 mg) twice daily, fluconazole (200 mg) once daily, and acyclovir (400 mg) 3 times daily orally.

The swabs for fungal cultures collected from the oral cavity, pharynx, epiglottis, and sputum were analyzed. Sabouraud dextrose agar plates were used to assure purity and optimal growth of isolates. Species identification was confirmed using Auxacolor™ 2 (Bio-Rad) or Vitek (Bio-Merieux) identification system.

During *C. albicans* infections, patients received antifungal therapy consisting of caspofungin, voriconazole, or micafungin; infections caused by *C. glabrata* or *C. krusei* were treated using itraconazole; *Saccharomyces* and *Aspergillus* infections were treated using voriconazole or liposomal amphotericin B.

Statistical analysis

The statistical analysis was performed using Student's t-test and nonparametric χ^2 test with Yates's correction. The statistically significant difference between groups was assessed at the level of $p \leq 0.05$.

Results

There were no statistically significant differences between ages of autologous and allogeneic HSCT recipients. Differences in age were observed only between RD-BMT and URD-BMT groups ($p=0.023$). The most frequent diseases among autologous HSCT recipients were multiple myeloma (46.2% cases), non-Hodgkin lymphoma (29.6% cases), and Hodgkin lymphoma (19.3% cases). Acute myeloid leukemia was the most common in allogenic HSCT recipients (34.5% cases allogenic RD-BMT and 41.5% cases in allogenic URD-BMT patients).

The overall rate of fungal colonization in patients undergoing HSCT was 8.7% (Table 2). Patients undergoing allogeneic HSCT (RD-BMT 17.9%, URD-BMT 11.2%) were colonized significantly more often compared to autologous HSCT recipients (4.7%) ($p<0.0001$). There were no statistically significant differences between fungal colonization in RD-BMT and URD-BMT patients ($p=0.19$) (Table 2).

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Table 1. Characteristics of the study group.

Characteristics	HSCT type					
	Autologous – HSCT		Allogeneic – RD-BMT		Allogeneic – URD-BMT	
No. of patients (%)	301	(100%)	84	(100%)	188	(100%)
Age, mean years (range)	50.81	(19–74)	41.58	(20–66)	37.16	(18–67)
Sex						
Male	174	(57.8%)	45	(53.6%)	95	(50.5%)
Female	127	(42.2%)	39	(46.4%)	93	(49.5%)
Diagnosis						
Acute myeloid leukemia	0	(0%)	29	(34.5%)	78	(41.5%)
Acute lymphoid leukemia	1	(0.3%)	16	(19%)	51	(27.1%)
Chronic myeloid leukemia	1	(0.3%)	8	(9.5%)	11	(5.9%)
Chronic lymphoid leukemia	1	(0.3%)	4	(4.8%)	4	(2.1%)
Non-Hodgkin lymphoma	89	(29.6%)	3	(3.6%)	1	(0.5%)
Hodgkin lymphoma	58	(19.3%)	3	(3.6%)	3	(1.6%)
Multiple myeloma	139	(46.2%)	0	(0%)	0	(0%)
Severe aplastic anemia	0	(0%)	4	(4.8%)	24	(12.8%)
Myelodysplastic syndrome	0	(0%)	7	(8.3%)	9	(4.8%)
Myelofibrosis	0	(0%)	10	(11.9%)	7	(3.7%)
Others	12	(4%)	0	(0%)	0	(0%)

HSCT – hematopoietic stem cell transplantation; RD-BMT – allogeneic HSCT recipients related donor; URD-BMT – allogeneic HSCT recipients unrelated donor.

Table 2. Mucosal colonization with fungal species among HSCT patients.

Species	Site			
	HSCT type			Total n=573 (100%)
	Autologous – HSCT n=301 (100%)	Allogeneic – RD-BMT n= 84 (100%)	Allogeneic – URD-BMT n=188 (100%)	
Oral cavity	0 (0%)	5 (6%)	5 (2.7%)	10 (1.7%)
C. albicans	0	5	4	9
C. krusei	0	0	1	1
Pharynx	12 (4%)	9 (10.7%)	12 (6.4%)	33 (5.8%)
C. albicans	9	6	6	21
C. krusei	0	1	2	3
C. glabrata	1	1	1	3
C. famata	0	1	1	2
Aspergillus sp.	1	0	0	1
Saccharomyces cerevisiae	0	0	2	2
C. albicans + *Saccharomyces cerevisiae*	1	0	0	1
Epiglottis	0 (0%)	0 (0%)	1 (0.5%)	1 (0.2%)
C. krusei	0	0	1	1
Sputum	2 (0.7%)	1 (1.2%)	3 (1.6%)	6 (1%)
C. albicans	1	0	0	1
C. krusei	1	1	2	4
Saccharomyces cerevisiae	0	0	1	1
Total	**14 (4.7%)**	**15 (17.9%)**	**21 (11.2%)**	**50 (8.7%)**

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Table 3. Fungal infections – species distribution of isolates collected from HSCT patients.

Species	HSCT type									Total n=573 (100%)
	Oral cavity			Pharynx			Sputum			
	Auto-HSCT n=301 (100%)	RD-BMT n=84 (100%)	URD-BMT n=188 (100%)	Auto-HSCT n=301 (100%)	RD-BMT n=84 (100%)	URD-BMT n=188 (100%)	Auto-HSCT n=301 (100%)	RD-BMT n=84 (100%)	URD-BMT n=188 (100%)	
C. albicans	3	2	5	4	11	9	2	4	5	45 (7.9%)
C. krusei	0	2	1	2	4	6	0	1	2	18 (3.1%)
C. glabrata	0	2	1	4	4	12	2	1	2	28 (4.9%)
C. famata	0	1	0	0	0	0	0	0	0	1 (0.2%)
C. sphaerica	0	0	0	0	1	0	0	0	0	1 (0.2%)
C. tropicalis	0	0	0	0	0	1	0	0	0	1 (0.2%)
Candida sp.	0	0	1	0	0	0	0	0	0	1 (0.2%)
Aspergillus sp.	0	0	0	0	0	0	0	1	1	2 (0.3%)
Saccharomyces cerevisiae	0	0	0	0	0	1	0	0	0	1 (0.2%)
C. albicans + *C. tropicalis*	0	0	0	1	0	1	0	0	0	2 (0.3%)
C. albicans + *C. krusei*	0	0	0	0	0	1	0	1	0	2 (0.3%)
C. albicans + *C. glabrata*	0	0	0	0	0	2	0	0	0	2 (0.3%)
C. albicans + *Saccharomyces cerevisiae*	0	0	0	0	0	1	0	0	1	2 (0.3%)
C. krusei + *Saccharomyces cerevisiae*	0	0	1	0	0	1	0	1	0	3 (0.5%)
Total	**3 (1%)**	**7 (8.3%)**	**9 (4.8%)**	**11 (3.7%)**	**20 (23.8%)**	**35 (18.6%)**	**4 (1.3%)**	**9 (10.7%)**	**11 (5.9%)**	**109 (19%)**

Colonizing cultures were *C. albicans* (pharynx: 21 isolates, oral cavity: 9 isolates, sputum: 1 isolate), *C. krusei* (sputum: 4 isolates, pharynx: 3 isolates, oral cavity and epiglottis: 1 isolate each), and sporadically *C. glabrata*, *C. famata*, *Aspergillus spp*., and *Saccharomyces cerevisiae*. A total of 14 (2.4%) of the 573 patients were colonized with *Candida* non-albicans species (Table 2).

The overall rate of fungal infection in HSCT recipients was 19%, with statistically significantly higher incidence among allogeneic patients than among the autologous group (p<0.001). Comparing fungal infection in different localizations between the 2 analyzed groups, we found that fungal infections were significantly more frequent in autologous than allogeneic patients: oral cavity 5.88% *vs.* 1% (p=0.002), pharynx 20.22% *vs.* 3.7% (p<0.001), and sputum 7.35% *vs.* 1.3% (p=0.001). There were no statistically significant differences between RD-BMT and URD-BMT groups in any localizations.

Analysis of species distribution of isolates collected from HSCT patient. *C. albicans* was the most frequent species found in isolates from pharynx, sputum and oral cavity collected from patients undergoing HSCT (7.9%), followed by *C. glabrata* (4.9%) and *C. krusei* (3.1%). *Non-albicans Candida* cultures were collected from 50 patients (8.7%). Aspergillosis was more common after allogeneic than after autologous HSCT. In 11 patients (1.9%) infection was caused by more than one pathologic strain. The pharynx was the most frequently colonized site (Table 3).

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Table 4. Species selection during fungal infections therapy – autologous HSCT.

Secondary isolate	Primary isolate						
	Autologous – HSCT						
	C. albicans	*C. krusei*	*C. glabrata*	*C. tropicalis*	*C. famata*	*Aspergillus* sp.	*Trichosporon asahii*
C. albicans		0	1	0	0	1	0
C. krusei	1		0	0	0	0	0
C. glabrata	1	0		0	0	0	0

Table 5. Species selection during fungal infections therapy – allogenic – RD-BMT.

Secondary isolate	Primary isolate						
	Allogenic - RD-BMT						
	C. albicans	*C. krusei*	*C. glabrata*	*C. tropicalis*	*C. famata*	*Aspergillus* sp.	*Trichosporon asahii*
C. albicans		1	0	1	0	0	1
C. glabrata	1	0		0	1	0	0
C. sphaerica	0	0	1	0	0	0	0
C. krusei and *Saccharomyces cerevisiae*	1	0	0	0	0	0	0

Table 6. Species selection during fungal infections therapy – allogenic – URD-BMT.

Secondary isolate	Primary isolate								
	Allogenic – URD-BMT								
	C. albicans	*C. krusei*	*C. para-psilosis*	*C. dubli-nensis*	*C. glabrata S. cerevisiae*	*Aspergillus* sp.	*C.tropicalis S. cerevisiae*	*S. cerevisiae C. krusei C. kefyr*	*C. albicans C. albicans C. spherica C. lusitaniae C. albicans*
C. albicans		2	0	0	0	1	0	3	0
C. krusei	1		1	1	2	0	0	0	1
C. glabrata	4	0	0	0	0	0	0	0	0
S. cerevisiae	0	1	0	0	0	0	0	0	0
C. albicans C. glabrata	0	0	0	0	0	0	2	0	0

In 30 out of 109 (4.7%) HSCT patients with fungal infections receiving antifungal treatment, a selection of species were observed: in 4 cases after autologous and in 26 after allogeneic transplantation (Tables 4–6).

Discussion

In our study, the overall rate of fungal colonization was lower than the rates of 28–57% reported by others and there were no differences in species distribution [8,9,12–14]. Latest

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multicenter study of Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) showed that the percentage of invasive fungal infections (IFI) among patients undergoing HSCT was lower than in earlier studies [15]. The rate of oral and intestinal colonization can vary over time, not only in the study population overall but in individual patients as well, and it seems to be a dynamic process [14]. In our study we also evaluated the site of fungal colonization. The most frequent one was pharynx followed by oral cavity. Epiglottis and sputum were rare sites where fungi could be isolated from.

Allogeneic HSCT is an important predictor of fungal infection associated with a worse prognosis than autologous HSCT because of defects in cell-mediated immunity. In our study the percentage of fungal infections among this group of patients was higher. Our results are consistent with those of other authors [15,16]. The immunological status of the host is the most significant factor in host-pathogen interaction [5,7,17,18].

Neutropenia and mucosal toxicity resulting from conditioning regimen are the main risk factors during early transplant period (first 30 days), while immunosuppressive therapy for GvHD in the later stage [19]. The risk is increasing due to intensity of treatment for hematological malignancies. Risk factors comprise: high-dose chemotherapy, radiotherapy and immunosuppressive regimens. A study of Srinivasan et al. revealed that the first period (0–30 days) after bone marrow transplantation was associated with a higher risk of bacterial infections. Patients with acute GvHD were at higher risk of fungal infections in later periods (31–100 and 101–730 days). Chronic GvHD and older age was associated with a greater risk of fungal infections between 101–730 days following the transplantation [20].

Intensive timing induction therapy in children with acute myeloid leukemia was connected with more frequent and more fatal fungal and bacterial infections compared with standard timing induction therapy [21]. Similar results were obtained when intensification of treatment in infants with acute lymphoblastic leukemia was performed [22]. The routine antifungal prophylaxis in pediatric patients still remains a topic of controversy [23]. Obtaining a timely laboratory confirmed diagnosis of fungal infection is often difficult and some researchers evaluating their patients distinguish proven and probable fungal infection [15].

Our data confirm that *C. albicans* is the most frequent fungal pathogen responsible for majority of mucosal and disseminated *Candida* infections [9,24]; however, in some reports the incidence of candidemia has decreased probably due to prophylaxis with fluconazole [9]. In our study, despite antifungal prevention regimen of fluconazole, *Candida* infections remained a major problem in HSCT patients. It was speculated that Dectin-1 mediated mechanisms was responsible for increased *Candida* colonization in hematopoietic stem cell transplant recipients [13]. Over the last 2 decades the spectrum of fungal infections has changed with a notable shift from *C. albicans* to *Non-albicans Candida* strains [25,26]. At the same time increase of invasive infections caused by *Aspergillus* species was observed [5]. In our population infections due to *Aspergillus* species were extremely rare.

Prophylaxis can be used to prevent invasive infections but also can favor the onset of heavy, aggressive ones and induce selection of drug-resistant strains. The influence on the distribution of different *Candida* species is also notable. With the widespread use of fluconazole in the 1990s as prevention regimen in high risk patients including HSCT recipients, the incidence of invasive candidiasis decreased but IFI (invasive fungal infections) became a major cause of mortality [9,26,27]. Several studies reported that fluconazole-resistant species seemed to have been disproportionately represented among bone marrow transplant patients [9,29,30]. Nowadays new approaches of antifungal prophylaxis are being developed. Triazoles (voriconazole or posaconazole) are thought to be drugs of choice for antifungal prophylaxis if there are no contraindications [31]. Amphotericin B deoxycholate inhalation prophylaxis against invasive aspergillosis seems to be a promising approach [32]. Guidelines for primary antifungal prophylaxis for pediatric patients undergoing HSCT have been recently published [33].

Marr et al. have demonstrated that fluconazole prophylaxis selected for fluconazole-resistant *Candida* species, possibly leading to fungemia acquired endogenously via the gastrointestinal tract [9]. In our series in 30 patients (4.7%) receiving antifungal treatment the selection of species was observed with appearance of uncommon strains. It seems that antifungal susceptibility testing of isolates should be recommended prior to treatment of infection to make an optimal therapeutic decision and obtain quick curative effect.

In HSCT patients it is very important to preserve balanced mucosal microecology, especially intestinal with low *Candida* counts. Disruption of the microflora by antimicrobial therapy leads to increased *Candida* positivity in stool cultures and increased intestinal *Candida* counts [34,35], as well as increased *Candida* colonization [14] and in later consequences to invasive candidiasis in patients with neutropenia.

Studies performed in recent years focused on recognition of genetic variables which can be helpful in risk prediction for IFI in patients with hematological malignancies and HSCT. Toll-like receptor 4 (TLR4), interleukins: IL-1 gene cluster, IL-10 and plasminogen were reported as associated with the risk for documented invasive aspergillosis [36–40]. The development of this knowledge based on large studies with translation into

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clinical practice may allow predicting risks for IFI and use of the best preventive strategies.

Conclusions

C. albicans is the main pathogen involved in fungal colonization and infections in HSCT patients. Allogeneic HSCT recipients are more susceptible to fungal infections compared to the autologous group.

The intense development of hematological malignancies treatment connected with increased proportion of unrelated donors and HLA-mismatched transplants, intense immunosuppression, and better survival rate during early transplant period predispose to infectious complications.

Selection of species during prophylaxis and antifungal therapy, increased number of infections caused by drug-resistant fungal species, and poor outcomes emphasize the need to develop more effective prevention and treatment strategies based on new antifungal drugs and microbe-specific diagnoses.

Conflicts of interest

The authors declare that they have no conflict of interest.

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