Medical Mycology January 2011, **49**, 26–31

informa
healthcare

Evaluation of species distribution and risk factors of candidemia: A multicenter case-control study

NUR YAPAR*, HUSNU PULLUKCU†, VILDAN AVKAN-OGUZ*, SELDA SAYIN-KUTLU‡, BULENT ERTUGRUL§, SUZAN SACAR‡, BANU CETIN# & ONUR KAYA^

**Infectious Diseases and Clinical Microbiology, Dokuz Eylul University, Izmir, †Infectious Diseases and Clinical Microbiology, Ege University, Izmir, ‡Infectious Diseases and Clinical Microbiology, Pamukkale University, Denizli, §Infectious Diseases and Clinical Microbiology, Adnan Menderes University, Aydin, #Infectious Diseases and Clinical Microbiology, Celal Bayar University, Manisa, and ^Infectious Diseases and Clinical Microbiology, Suleyman Demirel University, Isparta, Turkey*

This study was planned to determine the risk factors of candidemia, and the most common *Candida* species causing bloodstream infections. A case-control study which included adult patients was conducted over a 1-year period at tertiary-care educational hospitals in Turkey. A total of 83 candidemia episodes were identified during the study period. *Candida albicans* was the most common species recovered (45.8%) followed by *Candida tropicalis* (24.1%) *Candida parapsilosis* (14.5%) and *Candida glabrata* which was isolated from only four (4.8%) patients. Presence of a urethral catheter (odds ratio [OR] 2.38; 95% confidence interval [CI] 1.09–5.19; $P = 0.02$), previous use of antibiotics (OR 2.61; 95% CI 1.05–6.46; $P = 0.03$), RBC transfusions (OR 2.14; 95% CI 1.16–3.94; $P = 0.01$) and parenteral nutrition (OR 4.44; 95% CI 2.43–8.11; $P < 0.01$) were found as independent risk factors for candidemia. TPN (Total Parenteral Nutrition) was an independent risk factor for both *C. albicans* and non-*Candida albicans Candida* species ($P < 0.001$). Most of the risk factors were invasive procedures and former medications. We conclude that a great number of candidemia cases are preventable by means of reduction of unnecessary invasive procedures and the use of antimicrobials.

Keywords Candidemia, *C. albicans*, non-*Candida albicans Candida* species, risk factors

Introduction

In recent years, *Candida* species have emerged as major causes of infections among patients with serious underlying diseases such as hematological malignancies or critically ill patients hospitalized in Intensive Care Units (ICUs). Those infections have raised concerns as a result of high mortality rates and medical costs [1,2]. *Candida* spp. are the fourth leading cause of nosocomial bloodstream infections (BSIs) in the United States (US) and sixth in Turkey [3–5]. The incidence of candidemia per 1,000 admissions varies between 0.17 (in general hospitals) and 20 (in ICU patients) in European countries [6]. It ranges from 6–24 per 100,000 population per year in US [2]. In a study conducted between 2000 and 2003 in our country, it was found that the incidence of candidemia was 0.56 per 1,000 hospital admissions per year and there was a statistically significant increase in the incidence of candidemia caused by non-*Candida albicans Candida* species [7].

Although in recent years *Candida albicans* is responsible for more than half of the cases of candidemia, the ratio of infections due to non-*Candida albicans Candida* species has gradually increased. Some possible risk factors, such as fluconazole prophylaxis, underlying hematological malignancies or patient's age were identified in previous studies. However, there are still limited data about factors associated with infections due to non-*Candida albicans Candida* species [2,6,8].

Several non-*Candida albicans Candida* species are resistant to or have decreased susceptibility to fluconazole *in vitro*, although the clinical relevance of this information is not well defined. On the other hand, as fluconazole is generally effective against *C. albicans,* it is a safe and inexpensive treatment of choice [9]. Determining risk factors associated with BSIs caused by *C. albicans* and non-*Candida albicans*

Received 14 January 2010; Received in final revised form 24 March 2010; Accepted 11 June 2010

Correspondence: Nur Yapar, Dokuz Eylul University, Infectious Diseases and Clinical Microbiology, Izmir, Turkey. E-mail: nuryapar@gmail.com

DOI: 10.3109/13693786.2010.501344

Candida species, which was one of the aims of our study, can provide guidance in deciding on empirical anticandidal therapy.

In Turkey, there are limited reports documenting the spectrum of yeasts responsible for candidemia and risk factors, therefore we conducted an observational, multi-center, case-control study to investigate causative agents and risk factors of candidemia in adult patients at six tertiary-care educational hospitals.

Methods

Study design and patient selection

An observational, prospective, case-control study was conducted from February 2008 to the end of January 2009 with the aim of analyzing *Candida* species causing candidemia and their risk factors in six Turkish tertiary-care educational hospitals. The study included patients older than 18 years of age with *Candida* BSIs, the latter being defined as isolation of any species of *Candida* in at least one blood culture of patients who presented with clinical signs or symptoms of infection [10]. We randomly selected at least two control patients for each case who were matched according to the age groups hospitalized in the same hospital in the same period with no signs and symptoms of candidemia and with negative blood cultures for *Candida* spp.

Data collection

Study team members from each hospital collected demographic and clinical data by reviewing patients' medical reports. Since the study was an observational noninterventional investigation, all decisions regarding patient management including the diagnostic tests and antifungal treatment were made by the patients' physicians and not by the research team members. The case group data used for risk factor analyses were collected up to the time of the development of candidemia and the data for controls were collected up to the same day. Risk factors for the last 30 days prior to onset of candidemia were assessed. The parameters collected for each case and controls included age, gender, length of stay (LOS) in the hospital. In addition, we considered the presence of predisposing factors such as diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease (COPD), malignancy, organ transplantation, surgical procedures, presence of central venous (CVC) or urethral catheters, mechanical ventilation, red blood cell (RBC) transfusion, administration of total parenteral nutrition (TPN), anticancer chemotherapy, steroids, antibiotics and antifungals. The Eastern Cooperative Oncology Group (ECOG) Performance Status was used to assess the patient's daily living abilities [11].

Identification of species

Blood cultures were processed at each of the hospitals participating in the study by an automated system (Bactec, Becton Dickinson, USA) and isolates were transferred to blood agar and Sabouraud dextrose agar. After the germ-tube test, yeasts were identified according to their morphology on cornmeal Tween 80 agar, colour on CHROMagar *Candida* (CHROMagar, France) and biochemical tests using API 20C AUX System (bioMérieux, France).

Statistical analyses

Categorical variables were evaluated using the chi-square and 2-tailed Fisher's exact tests. For continuous variables the t-test was used. Variables that were found as significant ($P < 0.05$) in these tests were considered as candidates for multivariate analysis. Multivariable, backwards stepwise, logistic regression analyses were built to identify independent risk factors for candidemia. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS, Version 15.0, Chicago, Il, USA) and CDC software EPI INFO (version 6.0, Atlanta, GA, USA).

Results

During the study period, 83 candidemia episodes in 83 patients were identified, of which 47 (56.6%) cases involved males with a mean age of 55.04 $\pm$ 17.04 (18–84) years as compared to 55.83 $\pm$ 16.56 (18–90) years of age in the control group. Thirty-three of the patients (39.7%) were hospitalized in intensive care units (ICUs), 26 (31.3%) in surgical wards and 24 (29%) were in medical wards. The median time interval between the initial hospitalization and the diagnosis of candidemia was 18 (1–191) days.

Distribution of species causing candidemia

C. albicans was recovered from 38 (45.8%) of the patients, whereas non-*Candida albicans Candida* species were isolated from 45 (54.2%). Among the latter yeasts, *Candida tropicalis* was the most frequently isolated, followed by *Candida parapsilosis*, *Candida glabrata* and *Candida kefyr*. Distribution of *Candida* species isolated from patients with candidemia is given in Table 1.

Risk factors associated with candidemia

Risk factors identified in univariate analyses associated with the occurrence of candidemia were length of hospitalization, high ECOG scores (3 or more), presence and duration of urethral and central venous catheters (CVC), central nervous system, thoracic or abdominal surgery, previous

Table 1 *Candida* species isolated from patients with candidemia.

Candida species	*n* (%)
Candida albicans	38 (45.8)
Candida tropicalis	20 (24.1)
Candida parapsilosis	12 (14.5)
Candida glabrata	4 (4.8)
Candida kefyr	3 (3.6)
Others	6 (7.2)

antibiotic and antifungal therapy, RBC transfusions and total parenteral nutrition (TPN). The patients' characteristics and risk factors for candidemia are given in Table 2.

In multivariate analysis, the presence of a urethral catheter, previous use of antibiotics, transfusion of RBC and parenteral nutrition were found as independent risk factors associated with candidemia as presented in Table 3.

Risk factors for candidemia due to C. albicans *and non-*Candida albicans Candida *species*

When the risk factors associated with candidemia caused by *C. albicans* were evaluated, it was found that significant differences existed between the clinically ill patients and the controls with respect to the following factors; previous use of broad spectrum antibiotics and any antifungal agent, history of at least one of the following surgical procedures: central nervous system, thoracic or abdominal surgery, transfusion of red blood cells (RBC), high ECOG scores (more than 2), neutropenia, presence of indwelling catheters, endotracheal intubation, mechanical ventilation and TPN. Among these risk factors we found no significant differences between the patients and controls in cases involving non-*Candida albicans Candida* species relative to surgical procedures, neutropenia, intubation and mechanical ventilation. Results of univariate analyses are given in Table 4.

In multivariate analysis, TPN, neutropenia and surgical procedures mentioned above were identified as independent risk factors for *C. albicans* infections, whereas TPN, previous usage of antibiotics and presence of urethral catheters were found to be important in non-*Candida albicans* candidemia cases. Details are presented in Tables 5 and 6.

Discussion

Distribution of species causing candidemia

In the present study we identified 83 candidemia episodes in 83 patients in which *C. albicans* was the most common isolate (45.8%) recovered from clinical specimens. However non-*Candida albicans Candida* species were associated in a higher ratio (54.2%) than *C. albicans* when they were considered together. Among non-*Candida albicans Candida*

Table 2 Patient characteristics and risk factors for candidemia.

Patient characteristics and risk factors	Cases ($n = 83$) *n* (%)	Controls ($n = 221$) *n* (%)	*P* values
Gender Male	47 (56.6)	120 (54.3)	0.716
Mean age ± SD (years)	55.04 ± 17.04	55.83 ± 16.56	0.713†
Underlying conditions			
Diabetes mellitus	15 (18.1)	47 (21.3)	0.538
Renal failure	13 (15.7)	30 (13.5)	0.642
Solid malignancy	18 (21.7)	50 (22.6)	0.861
Hematologic malignancy	10 (12.0)	23 (10.4)	0.681
Trauma*	11 (13.2)	22 (9.9)	0.410
Neutropenia	9 (10.8)	11 (4.9)	0.06
Hospitalization in the ICU	55 (66.3)	130 (58.8)	0.236
ECOG Score (3 or more)	75 (90.0)	154 (69.6)	**0.0001** **0.0001**§
LOS‡			
Mean ± SD (days)	30.47 ± 32.73	20.60 ± 28.24	**0.01**†
1–7 days	13 (15.7)	77 (34.8)	
8–14 days	22 (26.5)	55 (24.9)	**0.001**§
More than 14 days	48 (57.8)	89 (40.3)	
Invasive procedures			
Indwelling urethral catheter	72 (86.7)	133 (60.2)	**0.0001**
Duration of urethral catheterization (mean ± SD)	18.87 ± 29.30	8.62 ± 16.83	**0.004**†
CVC	57 (68.7)	83 (37.6)	**0.0001**
CVC duration (mean ± SD)	15.10 ± 23.08	5.84 ± 15.47	**0.001**†
Intubation	41 (49.4)	91 (41.2)	0.198
Tracheotomy	19 (22.9)	37 (16.7)	0.218
Mechanical ventilation	39 (47.0)	85 (38.5)	0.178
Duration of mechanical ventilation (mean ± SD)	9.10 ± 16.22	6.70 ± 17.34	0.275†
Major surgery#	43 (51.8)	74 (33.4)	**0.003**
Medications			
Previous use of antibiotics	76 (51.8)	74 (33.4)	**0.003**
Antibiotic combinations (2 or more)			
Previous use of antifungals	59 (77.6)	69 (43.6)	**0.0001**
RBC transfusion	15 (18.0)	16 (7.2)	**0.005**
TPN	60 (72.3)	102 (46.1)	**0.00004**
	49 (59.0)	42 (19.0)	**0.0001**

†t-test.
*Major thoracic or abdominal trauma.
‡Length of stay.
§Linear-by-Linear association.
#Central nervous system, thoracic or abdominal surgery.

Table 3 Multivariate logistic regression analysis of independent risk factors for candidemia.

Variables	*P*	OR	95% CI
Urethral catheterization	0.02	2.38	1.09–5.19
Previous use of antibiotics	0.03	2.61	1.05–6.46
RBC transfusion	0.01	2.14	1.16–3.94
TPN	<0.001	4.44	2.43–8.11

OR: Odds Ratio; CI: Confidence interval.

species, *C. tropicalis* was the most frequently recovered pathogen followed by *C. parapsilosis*, *C. glabrata* and *C. kefyr*. Although the frequency of *Candida* species varies according to the geographical setting, a decreasing trend in the isolation of *C. albicans* has been noted worldwide [2,6,12].

In the ARTEMIS DISK Surveillance program conducted between 1997 and 2003, increased rates of infections caused by *C. tropicalis* and *C. parapsilosis* were observed although there were no significant changes in the isolation rates of *C. glabrata* and *C. krusei* [9]. In the European Confederation of Medical Mycology (ECMM) survey, incidence rates were 14% for *C. glabrata* and *C. parapsilosis* infections, 7% for *C. tropicalis* and 2% for *C. krusei* [13,14].

In our study, the distribution of *Candida* species was generally similar to reports from European countries. An exception is the frequency of *C. tropicalis* which was the second most common species isolated from our cases. *C. tropicalis* is an important pathogen in patients with hematological malignancies and in the US, the frequency of this yeast in clinical cases apparently decreased as a result of the use of fluconazole prophylaxis. However, in other countries, especially in Latin America and Asia-Pasific region, *C. tropicalis* is more common [2,6,15,16]. Xess *et al.*, reported that *C. tropicalis* was the most frequently isolated species during a 5-year study period in North India [17]. Similarly, in a retrospective investigation conducted in one of our study hospitals between 2000 and 2003, *C. tropicalis* was the most common non-*Candida albicans Candida* species (20.2%) identified, followed by *C. parapsilosis* (12.5%), *C. guilliermondii* (3.8 %) and *C. glabrata* (3.8%) [7]. This frequent isolation of *C. tropicalis* in our study population could be explained, in part, by the lower ratio of patients receiving fluconazole prophylaxis and geographical features [2,6,7]. *Candida glabrata* which is one of the fluconazole resistant non-*Candida albicans Candida* species was responsible for only four candidemia episodes in our patients. This species has emerged as an important fungal pathogen in the US accounting for 20–24% of all *Candida* BSIs [2]. In contrast, in most surveys from European countries and from Latin America, lower frequencies of *C. glabrata* infections were reported [6,15,18]. In two reports from our country, *C. glabrata* was isolated from 5% and 8.8% of patients hospitalized in tertiary care hospitals [19,20]. The reasons for these different frequencies in different countries are not clear but may include exposure to azoles, patients' age, geographical features and the sensitivity of blood culture media used in the study [2,6,8].

Risk factors associated with candidemia

Risk factors involved in candidemia can be divided into (i) host-related factors such as chronic renal failure, diabetes mellitus, trauma or other immunocompromising conditions and (ii) healthcare-related factors such as hospitalization

Table 4 Risk factors for candidemia due to *Candida albicans* and non-*Candida albicans Candida* spp.

	Albicans Candidemia ($n = 38$)		Controls	Non-*Candida albicans* Candidemia ($n = 45$)	
Risk factors	*n* (%)	*P* values	($n = 221$)	*P* values	*n* (%)
Antibiotic use	33 (86.8)	**0.04**	158 (71.5)	**0.001**	43 (95.6)
Combination antibiotherapy (more than one)	27 (81.8)	**0.0001**	69 (43.7)	**0.0001**	69 (43.7)
Antifungal use	7 (18.4)	**0.02**	16 (7.2)	**0.02**	8 (17.8)
Major surgery	23 (60.5)	**0.001**	74 (33.4)	0.160	20 (44.4)
RBC transfusion	30 (78.9)	**0.0001**	102 (46.1)	**0.01**	30 (76.7)
ECOG Score (3 or more)	35 (92.1)	**0.004 (0.002)****	154 (69.6)	**0.008 (0.005)****	40 (88.8)
Neutropenia	6 (15.7)	**0.02**	11 (4.9)	0.643	3 (6.7)
Urethral catheter	31 (81.6)	**0.01**	133 (60.2)	**0.0001**	41 (91.1)
Central venous catheter	27 (71.1)	**0.0001**	83 (37.6)	**0.0001**	30 (66.7)
Intubation	23 (60.5)	**0.02**	91 (41.2)	0.884	18 (40.0)
Mechanical ventilation	23 (60.5)	**0.01**	85 (38.5)	0.714	16 (35.6)
Total parenteral nutrition	23 (60.5)	**0.0001**	42 (19.0)	**0.0001**	26 (57.8)

*Fisher's Exact Test.
**Linear-by-Linear Association.

Table 5 Multivariate logistic regression analysis of independent risk factors for *Candida albicans* candidemia.

Variables	*P*	OR	95% CI
TPN	<0.001	5.76	2.46–13.52
Neutropenia	0.001	18.02	3.30–98.33
Major surgery	0.04	2.49	1.09–5.97

in the ICU, presence of CVCs, parenteral nutrition, antibiotic therapy, antifungal prophylaxis or surgical procedures [1]. In our patients, presence of urethral catheterization, previous use of antibiotics, RBC transfusions and TPN were identified as independent risk factors of candidemia. However, unlike other studies in the literature, we did not find length of hospitalization, CVC use, colonization with *Candida* spp., hemodialysis, antifungal prophylaxis, mechanical ventilation, neutropenia or trauma as independent risk factors [4,21–23]. Besides previously described host-related risk factors such as chronic underlying diseases or immunocompromising conditions, we found no statistically significant differences with respect to underlying patient conditions between cases and controls [1,22]. It is interesting that use of CVCs was not found to be an independent risk factor in our study. We concluded that risk factors associated with candidemia could be related to the causative agents. In our study *C. albicans* was the most common pathogen followed by *C. tropicalis*. *Candida parapsilosis* known as an agent of catheter-related fungemia was not common (14.5 %) and moreover, 60.3 % of our patients were hospitalized out of the ICU where CVCs are infrequently used.

Risk factors for candidemia due to C. albicans *and non-*Candida albicans *species*

When we performed multivariate analyses of risk factors for BSIs caused by *C. albicans* and non-*Candida albicans Candida* species, TPN was an independent risk factor for candidemia caused these yeasts ($P < 0.001$). Additionally, an increased risk of *C. albicans* BSIs was independently associated with neutropenia ($P = 0.001$) and surgical procedures ($P = 0.04$) whereas previous antibiotic use ($P = 0.03$) and urethral catheterization ($P = 0.03$) were associated with an increased risk of developing non-*Candida albicans Candida* candidemia. However some risk factors such as neutropenia and usage of antifungal drugs were rare in our study population. For that reason we were not confident to evaluate them as statistically significant or not.

Table 6 Multivariate logistic regression analysis of independent risk factors for non-*Candida albicans* candidemia.

Variables	*P*	OR	95% CI
TPN	<0.001	3.98	1.93–8.20
Previous antibiotic use	0.03	5.04	1.13–22.47
Urethral catheter	0.03	3.27	1.06–10.03

In a 5-year review of fungemia in Thailand, authors found that former bacteremia and presence of fungal colonization were significantly more common in patients with *C. albicans* candidemia than those with non-*Candida albicans Candida* candidemia [16]. In a prospective study performed in the ICU of a tertiary care hospital in Athens, the authors noted that administration of glucocorticoids, presence of CVCs and candiduria were independent risk factors with respect to candidemia caused by non-*Candida albicans Candida* species [24]. Chow *et al*. reported that ICU patients having major surgical operations, gastrointestinal procedures, enteric bacteremia, duration of TPN, number of hemodialysis days and RBC transfusions were associated with non-*Candida albicans Candida* candidemia [25]. For *C. albicans* candidemia major surgery, enteric bacteremia, TPN duration and number of hemodialysis days were independent risk factors in this study. In a prospective nationwide study reported from Australia, former exposure of antifungal drugs, gastrointestinal surgical procedures, increasing age and intravenous drug use were found to be associated with non-*Candida albicans Candida* candidiemia. Most common non-*Candida albicans Candida* species isolated in this study was *C. glabrata* and this could be an explanation for risk factor about age [26].

There are numerous studies investigating epidemiology and risk factors of candidemia in the English literature. However, most of them have been conducted in ICUs or hematology/oncology units and patients involved in these studies had some specific underlying conditions such as hematological or solid malignancies. Some of these studies included patients with only candidemia and analyses of risk factors or prognostic indicators were conducted without control groups. For these reasons, results from these studies could be different in terms of risk factors. In our study we selected at least two control patients for each cases hospitalized in the same hospital ward in order to compare risk factors for candidemia. To our knowledge this is the first case-control and multicenter study investigating the epidemiology and risk factors of candidemia from Turkey.

Our study has some limitations. Possible predisposing conditions such as hemopoietic stem cell or solid organ transplantation, malignancy, trauma, intravenous drug abuse and renal failure were rare and these factors were not found to be independently related to candidemia despite the fact that they had been defined in previous studies. Additionally, we could not investigate the distribution of *Candida* species in these specific conditions. Furthermore, we did not perform long-term follow up investigations of the patients after diagnosis of candidemia. Therefore

we cannot provide conclusions about mortality rates of different *Candida* species and risk factors affecting mortality.

We observed that the most common cause of candidemia was *C. albicans* in our patient group. Non-*Candida albicans Candida* species were more frequent etiologic agents than *C. albicans* when they were considered together. The most common non-*Candida albicans Candida* species was *C. tropicalis*. Additionally species known to be more resistant to antifungal agents such as *C. glabrata* were rare. Important risk factors for candidemia were invasive procedures and therapeutic interventions such as urethral catheterization, parenteral nutrition, transfusion of RBC and usage of antimicrobial agents. We conclude that a great number of candidemias are preventable infections by reducing unnecessary invasive procedures or antimicrobials. However, further prospective studies with greater number of patients belonging to different risk groups should be planned in order to investigate the factors associated with infections caused by each *Candida* species.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1 Richardson MD. Changing patterns and trends in systemic fungal infections. *J Antimicrob Chemother* 2005; **56**(Suppl. S1): i5–i11.
2 Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin Microbiol Rev* 2007; **20**: 133–163.
3 Pappas PG. Invasive candidiasis. *Infect Dis Clin N Am* 2006; **20**: 485–506.
4 Bassetti M, Trecarichi EM, Righi E, *et al*. Incidence, risk factors, and predictors of outcome of candidemia. Survey in 2 Italian university hospitals. *Diag Microbiol Inf Dis* 2007; **58**: 325–331.
5 Inan D, Saba R, Yalcin AN, Yilmaz M, Ongut G. Device-associated nosocomial infection rates in Turkish medical-surgical intensive care units. *Infect Control Hosp Epidemiol* 2006; **27**: 343–348.
6 Lass-Flörl C. The changing face of epidemiology of invasive fungal disease in Europe. *Mycoses* 2009; **52**: 197–205.
7 Yapar N, Uysal U, Yucesoy M, Cakir N, Yuce A. Nosocomial bloodstream infections associated with *Candida* species in a Turkish university hospital. *Mycoses* 2006; **49**: 134–138.
8 Richardson M, Lass-Flörl C. Changing epidemiology of systemic fungal infections. *Clin Microbiol Infect* 2008; **14**(Suppl. 4): 5–24.
9 Pfaller MA, Diekema DJ, Rinaldi MG, *et al*. Results from the ARTEMIS DISK Global Antifungal Surveillance Study: a 6.5-year analysis of susceptibilities of *Candida* and other yeast species to fluconazole and voriconazole by standardized disk diffusion testing. *J Clin Microbiol* 2005; **43**: 5848–5859.
10 De Pauw B, Walsh TJ, Donnely JP, *et al*. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813–1821.
11 Oken MM, Creech RH, Tormey DC, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–655.
12 Abi-Said D, Anaissie E, Uzun O, *et al*. The epidemiology of hematogenous candidiasis caused by different *Candida* species. *Clin Infect Dis* 1997; **24**: 1122–1128.
13 Tortorano AM, Peman J, Bernhardt H, *et al*. Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. *Eur J Clin Microbiol Infect Dis* 2004; **23**: 317–322.
14 Tortorano AM, Kibbler C, Peman J, *et al*. Candidaemia in Europe: epidemiology and resistance. *Int J Antimicrob Agents* 2006; **27**: 359–366.
15 Colombo AL, Guimaraes T, Silva LRBF, *et al*. Prospective observational study of candidemia in Sao Paulo, Brazil: incidence rate, epidemiology, and predictors of mortality. *Infect Control Hosp Epidemiol* 2007; **28**: 570–576.
16 Anunnatsiri S, Chetchotisakd P, Mootsikapun P. Fungemia in non-HIV-infected patients: a five-year review. *Int J Infect Dis* 2009; **13**: 90–96.
17 Xess I, Jain N, Hasan F, Mandal P, Banarjee U. Epidemiology of candidemia in a tertiary care centre of north India: 5-year study. *Infection* 2007; **35**: 256–259.
18 Passos SX, Costa CR, Araujo CR, *et al*. Species distribution and antifungal susceptibility patterns of *Candida* spp. bloodstream isolates from a Brazilian tertiary care hospital. *Mycopathologia* 2007; **163**: 145–151.
19 Comert F, Kulah C, Aktas E, Eroglu O, Ozlu N. Identification of *Candida* species isolated from patients in intensive care unit and *in vitro* susceptibility to fluconazole for a 3-tear period. *Mycoses* 2006; **50**: 52–57.
20 Bakir M, Cerikcioglu N, Barton R, Yagci A. Epidemiology of candidemia in a Turkish tertiary care hospital. *APMIS* 2006; **114**: 601–610.
21 Guery BP, Arendrup MC, Auzinger G, *et al*. Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part I. Epidemiology and diagnosis. *Intensive Care Med* 2009; **35**: 55–62.
22 Ostorsky-Zeichner L, Pappas PG. Invasive candidiasis in the intensive care unit. *Crit Care Med* 2006; **34**: 857–862.
23 Bouza E, Munoz P. Epidemiology of candidemia in intensive care units. *Int J Antimicrob Agents* 2008; **32**(Suppl. 2): S87–S91.
24 Dimopoulos G, Ntziora F, Rachiotis G, Armaganidis A, Falagas ME. *Candida albicans* versus non-*albicans* intensive care unit-acquired bloodstream infections: Differences in risk factors and outcome. *Anesth Analg* 2008; **106**: 523–529.
25 Chow JK, Golan Y, Ruthazer R, *et al*. Factors associated with candidemia caused by non-*albicansCandida* species versus *Candida albicans* in the intensive care unit. *Clin Infect Dis* 2008; **46**: 1206–1213.
26 Playford GE, Marriott D, Nguyen Q, *et al*. Candidemia in nonneutropenic critically ill patients: risk factors for non-*albicansCandida* spp. *Crit Care Med* 2008; **36**: 2034–2039.

This paper was first published online on Early Online on 21 July 2010.