



## Original Article

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# ***Candidaemia in patients with haematological disorders and stem cell transplant***

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### **ABSTRACT**

The incidence of non-albicans species of *Candida* has recently increased, especially in patients with malignant haematological disorders receiving fluconazole prophylaxis. A retrospective study of patients who developed candidaemia at Riyadh Armed Forces Hospital between January 1992 and December 2002 was carried out. Thirty one episodes of candidaemia occurred in 27 patients with a variety of haematological disorders. Twenty-four episodes were caused by non-albicans species of *Candida*

and only 7 episodes were caused by *C.albicans*. The most frequent underlying haematological disorders were acute myeloid leukaemia (AML) followed by acute lymphoblastic leukaemia (ALL). The main predisposing factors for the development of candidaemia were: broad spectrum antibiotics, central venous catheters, neutropenia, cytotoxic chemotherapy, coexisting bacterial infections, steroid therapy, relapsing or untreated primary disease and fluconazole prophylaxis.

Eight episodes were complicated by chronic disseminated candi-

diasis. Amphotericin-B and amBisome were used in the treatment of Candida infections. The treatment was successful in 86% of the episodes of *C. albicans* and 50% of the episodes due to non-*albicans* species of Candida. The highest mortality rate was encountered with *C.tropicalis* infections.

Candidaemia is an important cause of mortality and morbidity in patients with malignant haematological disorders and stem cell transplant. The predominance of non-*albicans* species of Candida especially *C.krusei* and *C.tropicalis* is alarming. The early administration of appropriate antifungal therapy and the removal of infected intravascular catheters improve the outcome considerably.

## INTRODUCTION

Most fungal infections in hospitalized patients are caused by Candida species. Recently, there has been a substantial shift in the epidemiology of haematogenous candidiasis caused by different species [1-5]. The use of prophylactic fluconazole is known to decrease colonization and subsequent infection with *C. albicans*

[6,7]. However, the extensive use of this drug in neutropenic patients with leukaemia and stem cell transplant (SCT) has been associated with the emergence of azole-resistant non-*albicans* species of Candida [3-5,8-11].

Blood cultures for Candida become positive at a median time of 10 days after the onset of neutropenia [12]. Polymerase chain reactions (PCR) and antigen detection tests are useful in making an early diagnosis of candidaemia [13,14]. Successful management of candidaemia depends upon the early institution of antifungal therapy, the recovery of neutrophilic count and the early removal of intravascular catheters if present [12,15,16].

A previous study done at our institution demonstrated the predominance of non-*albicans* Candida in the bloodstream isolates in the haematology unit with *C. krusei* being the commonest Candida species encountered [17]. In view of that study and similar reports on the prevalence of non-*albicans* species of Candida in neutropenic patients with malignant haematological disorders, this retrospective study was conducted.

## PATIENTS, MATERIALS AND METHODS

Riyadh Armed Forces Hospital (RAFH) is a tertiary care center comprising 1200 beds with specialty services including: intensive care, haematology/oncology, SCT and solid organ transplantation. A retrospective study of patients with various haematologic disorders and SCT who developed candidaemia at RAFH between January 1992 and December 2002 was carried out. The medical records and the laboratory data of these patients were reviewed.

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## DEFINITIONS

**Candidaemia:** The presence of a clinical illness (eg. fever, hypotension or respiratory insufficiency) associated with the isolation of *Candida* species from at least one blood culture specimen, without evidence of visceral involvement. An episode was regarded as having at least one positive blood culture set for a single *Candida* species during one period of hospitalization. All the consecutive positive blood cultures within 72 hours for the same type of *Candida* during the same period of hospitalization were considered as a single episode. If more

than one *Candida* species were isolated during the same period of hospitalization, infection due to each species was considered a separate episode.

**Breakthrough fungaemia:** The presence of *Candida* in the bloodstream of patients who have received prophylactic systemic antifungal therapy for longer than 48 hours.

**Persistent infection:** The presence of *Candida* in blood culture specimens 72 hours or longer after starting appropriate antifungal therapy. All patients with persistent fungaemia were evaluated for secondary ocular, cardiovascular or joint infections.

**Chronic disseminated candidiasis (CDC):** The presence of histopathological evidence (budding yeast or pseudohyphae) of candidiasis in the spleen, the liver and the kidneys and/or radiological evidence (hypodense lesions) of hepatosplenic or renal candidiasis.

**Acute disseminated candidiasis (ADC):** Patients having evidence of multiple noncontagious organ infection acquired through haematogenous spread i. e. the presence of fungal infection (based on histology or culture) in a certain body organ and having clinical, histopathological or radiological evidence of the same

fungal infection in another organ.

**Catheter-related candidiasis:**

Candidaemia was considered to be catheter related if there is no apparent source of infection or if the organism was isolated from both central and peripheral blood culture specimens or if the organism was isolated from both a peripheral blood culture specimen and the tip of the central venous catheter.

**Colonization by Candida species:**

Positivity of surveillance cultures performed from nasal, pharyngeal, rectal, urinary and skin swabs.

**Other coexisting infections:**

The presence of other organisms (eg. bacteria, viruses or other fungal species) causing a clinically significant illness.

**Neutropenia:** Absolute neutrophilic count (ANC) <500 cells/mm<sup>3</sup> in the peripheral circulation was regarded as neutropenia and ANC <100 cells/mm<sup>3</sup> was regarded as profound or severe neutropenia. Duration of neutropenia was defined as the time interval in days from the onset of neutropenia till the detection of Candida species in blood culture specimens.

**Febrile illness:** More than two successive oral readings of greater than or equal to 38°C within 24 hours period.

**Therapeutic response (to both initial and subsequent therapy):**

The complete resolution of all signs and symptoms of infection and the presence of negative blood cultures for Candida.

**Therapeutic failure:** Failure of antifungal therapy to eliminate candidaemia within 3 days or no improvement or worsening of clinical manifestations after 3 days of antifungal therapy.

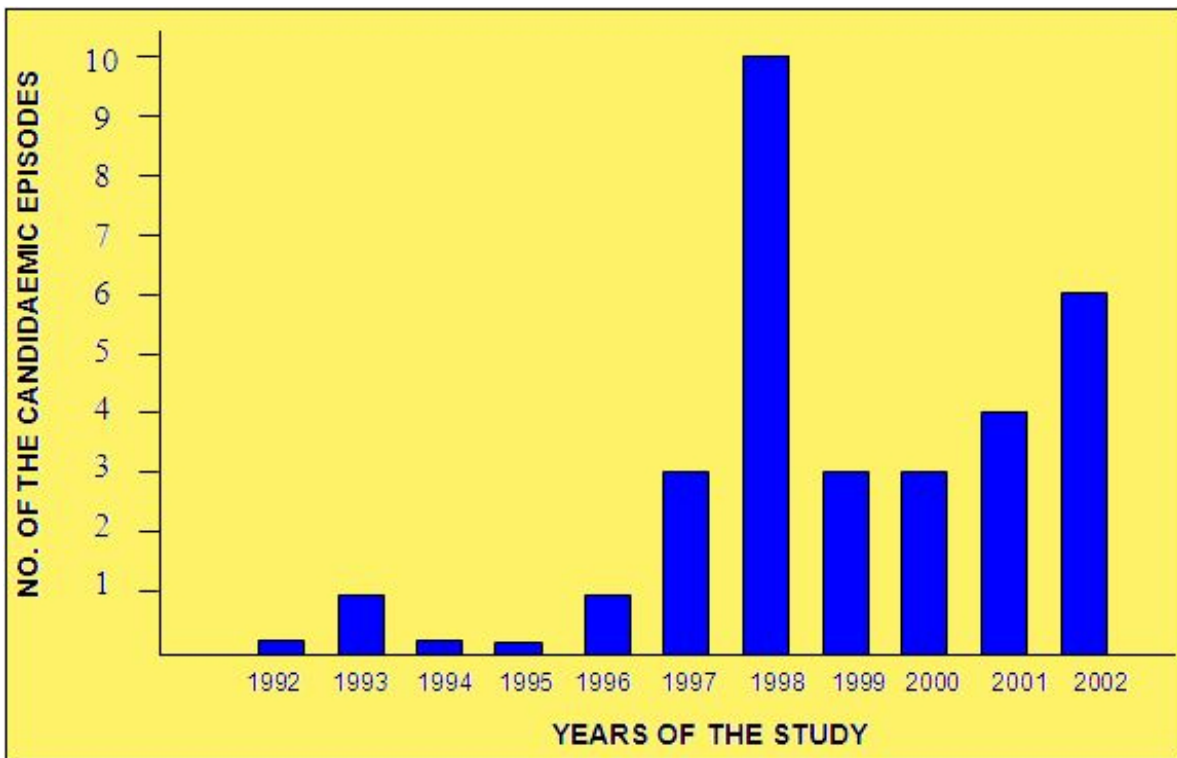
**Mortality:** Death attributable to fungaemia was considered when patients died with clinical, microbiological or histopathological evidence of active fungal infection in the absence of other identifiable causes of death.

**MICROBIOLOGICAL TECHNIQUES**

The diagnosis of candidaemia was based on the isolation of the yeast from one or more blood culture sets (aerobic and/or anaerobic bottles) collected from patients with various haematological disorders having febrile illness or clinical evidence of septic shock. Blood cultures were performed using the automated blood culture system (Bactec 9240, Becton Dickinson, USA]. Presumptive identification was done by the use of germ tube reaction, colony morphology and colour reac-

tion on chrom agar [Chrom Agar Technology, Paris]. Identification to species level was done by the commercial identification system API 20C [Analytic Products, plain view, NY, USA]. For CVC (central venous catheter) tip culture, a semiquantitative culture method was used where > 15 colony forming units were considered significant.

rienced three episodes of candidaemia with different species and two patients developed two episodes of fungaemia each. All the records of these patients were retrieved for analysis. All the positive blood cultures were thought to represent true infection rather than contamination. The distribution of the episodes of candidaemia over the study period of time is shown in Figure 1.



## RESULTS

Thirty one episodes of candidaemia were encountered in twenty-seven patients over an eleven year period (January 1992 to December 2002). One patient expe-

*Figure 1: Shows the distribution of the episodes of candidaemia*

Of the patients studied, 14 were males and 13 were females. The ages of these patients ranged between 16 and 72 years (mean:



36.8 years). Thirteen patients had AML, 10 had ALL, 2 non-Hodgkin's lymphoma, 1 multiple myeloma and 1 beta-thalassaemia major. Only 5 patients had SCT prior to the candidaemic episodes (4 allogeneic and 1 autologous). The overall incidence of candidaemia at our institution during the period of the study was 10.45% in patients with acute leukaemia and 4.4% in patients with SCT. Breakthrough fungaemia was seen in 15 episodes (2 episodes were caused by *C. albicans* and 13 episodes were caused by non-*albicans* species of *Candida*) during which patients were receiving fluconazole prophylaxis.

Acute disseminated candidiasis complicated one episode of fungaemia caused by *C. krusei* species. Only three episodes of candidaemia were complicated by persistent fungal infections (two with *C. krusei* and one with *C. tropicalis*). Amphotericin-B was used in the treatment of 19 of the episodes of fungaemia. The dose of amphotericin-B used was 1 mg per kg per day intravenously over 4 to 6 hours. Only 3 fungaemic episodes were treated with intralipid formulations of amphotericin-B (Abelcet; Enzon). Liposomal amphotericin-B (amBisome) was used in the treatment of 9 epi-

sodes of candidaemia and it was predominantly used in case of renal impairment or disseminated fungal infection. The doses of amBisome used were 3 to 5 mg per kg per day intravenously over 30 minutes. The duration of antifungal therapy was 2 to 3 weeks for uncomplicated candidaemia and 2 to 4 months for chronic disseminated candidiasis (CDC). Four cases of CDC were treated with amphotericin-B and 4 cases were treated with amBisome. All the patients who developed candidaemia and were having indwelling intravascular catheters in situ at the time of the fungaemic episode had removal of these devices.

Early removal of intravascular catheters (within 12 hours) was performed in 21 episodes, while late removal was done in the remaining 10 episodes of fungaemia. All 5 episodes of fungaemia due to *C. albicans*, during which early removal of indwelling intravascular devices was possible, ultimately had successful outcome, while only 10 of 16 episodes of non-*albicans* candidaemia, during which early removal of intravascular catheters was done, had successful outcomes. The predisposing factors for the development of candidaemia are

shown in Table 1.

Neutropenia, radiotherapy, steroid therapy and coexisting bacterial infections were more frequent with *C. albicans* infections while old age, other medical illnesses, relapsing disease, cytotoxic chemotherapy and fluconazole prophylaxis were more frequently encountered in episodes caused by non-*albicans* species. The coexisting bacterial infections were predominantly caused by gram negative organisms: *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Klebsiella pneumoniae* and *E. coli*. Compared to patients having fungaemia due to other types of non-*albicans* *Candida*, patients with *C. krusei* had a lower proportion of coexisting bacterial infections (41.7%) and a higher percentage of fluconazole use (75%). Nine patients with candidaemia (33.3%) had surgical intervention prior to the episodes of fungaemia. Twenty episodes of fungaemia (64.5%) were preceded by mucous membrane colonization. Relapsing primary haematological disorder was found to be a significant risk factor for the development of candidaemia (Fisher's exact, two sided  $p = 0.02$ ). Successful management of the candidaemic episodes was high-

er in *C. albicans* than in the other types of *Candida* (85.7% vs. 50%). Amongst the non-*albicans* species of *Candida*, the best outcome of treatment of the episodes of fungaemia was encountered with *C. parapsilosis* (100%). One year follow up of the 27 patients studied showed that 22 patients died and only 5 patients survived. The details are shown in Table 2.

Fungaemia was the primary cause of death in 37.5% of patients with non-*albicans* candidaemia but was the sole cause of death in one patient with *C. albicans* sepsis. The underlying haematological disorder and the development of other infections were the main causes of death in the deceased patients with *C. albicans* infections. Eight episodes of fungaemia were complicated by CDC (4 *C. albicans* and 4 non-*albicans* *Candida* species). In patients with CDC, the liver and the spleen were the most frequently involved internal body organs while involvement of the kidneys was encountered in only two episodes of candidaemia (Table 3).

## DISCUSSION

*Candida* species are the most common cause of fungal infec-

**Table 1: Shows the predisposing factors for candidaemia**

Risk Factors	C. albicans	Non-albicans Candida	C. krusei	C. tropicalis	C. parapsilosis	C. glabrata	C. famata	All Species
<b>Chemotherapy:</b>								
Not Given	2	3	1	0	1	1	0	5
1 - 3 Courses	1	9	6	3	0	0	0	10
4 or more Courses	4	12	5	3	2	1	1	16
<b>Broad Spectrum Antibiotics</b>	7	24	12	6	3	2	1	31
<b>Documented Bacterial Infection</b>	5	16	5	6	2	2	1	21
<b>Fluconazole Prophylaxis</b>	2	13	9	2	1	1	0	15
<b>Steroid Therapy</b>	6	10	6	3	1	0	0	16
<b>Radiotherapy</b>	4	4	2	1	1	0	0	8
<b>Neutropenia</b>	7	21	10	5	3	2	1	28
<b>Central Venous Catheters</b>	7	24	12	6	3	2	1	31
<b>Relapsing Disease</b>	3	11	6	3	1	0	1	14
<b>Other Medical Illnesses</b>	1	7	3	2	1	1	0	8
<b>Old Age</b>	0	4	2	1	0	1	0	4
<b>Mucocutaneous Colonization</b>	5	15	6	4	2	2	1	20



**Table 2: Shows certain characteristics of the candidaemic episodes**

<b>Species of Candida</b>	<b>Number of episodes</b>	<b>Septic shock</b>	<b>Artificial ventilation</b>	<b>Outcome of the episode</b>	<b>One year survival</b>	<b>Other coexisting infections</b>
<i>C. albicans</i>	7	4	3	6 successful	2	6
<i>C. krusei</i>	12	11	6	6 successful	5	11
<i>C. tropicalis</i>	6	5	2	2 successful	1	5
<i>C. parapsilosis</i>	3	2	1	3 successful	1	3
<i>C. glabrata</i>	2	2	1	1 successful	1	2
<i>C. famata</i>	1	1	1	0 successful	0	1
<b>Total</b>	<b>31</b>	<b>25</b>	<b>14</b>	<b>18 successful</b>	<b>10</b>	<b>28</b>

**Table 3: Shows causes of death and disseminated infections**

	<i>Candida albicans</i>	<i>Candida krusei</i>	<i>Candida tropicalis</i>	<i>Candida parapsilosis</i>	<i>Candida glabrata</i>	<i>Candida famata</i>	Non-albicans <i>Candida</i>	All <i>Candida</i> species
<b>Deceased Patients</b>	6	10	6	2	2	1	21	27
<b>Causes of Death</b>								
Primary Disease	1	4	0	0	1	0	5	6
Candidaemia	1	6	2	0	1	0	9	10
Primary Disease and Other Infections	3	0	4	2	0	1	7	10
Stem Cell Transplant Complications	1	0	0	0	0	0	0	1
<b>Chronic Disseminated Candidiasis</b>	4	2	1	1	0	0	4	8

tions and they produce infections that range from non-life threatening mucocutaneous illnesses to invasive processes that may eventually involve any body organ [9,16]. Candidaemia is a serious complication and an important cause of morbidity and mortality in patients with acute leukaemia, various forms of stem cell and solid organ transplantation [8-10,16]. The predisposing factors for candidaemia include: malignant haematological disorders specially AML, stem cell and solid organ transplantation, intensive cytotoxic chemotherapy, prolonged neutropenia, intravascular catheters, steroid therapy, broad spectrum antibiotic treatment, antifungal prophylaxis with fluconazole, bacteremia, cytomegalovirus disease, hospitalization and admission to intensive care units, HIV infection, surgical intervention and fetal immaturity [5,12,13,15,18-21]. Gastrointestinal colonization by *Candida* species has also been found to play a major role in the development of breakthrough candidaemia [5,8,15,22-24]. In addition, relapsing, untreated and refractory primary disease is an important associated factor for the development of fungaemia [25]. The predominant clinical manifestations of candidaemia are: fever, skin

lesions, respiratory symptoms and septic shock [12,15,20]. In our study, the main predisposing factors for the development of fungaemia were: malignant haematological disorders specially AML, broad spectrum antibiotics, central venous catheters, neutropenia, cytotoxic chemotherapy, coexisting bacterial infection and steroid therapy. In agreement with similar studies, fluconazole prophylaxis, mucocutaneous colonization by *Candida*, and relapsing primary malignant haematological disorder were found to be important predisposing factors for candidaemia, particularly in patients with fungaemia due to non-albicans species.

Previously, *C. albicans* was found to be the commonest cause of candidaemia, but in recent years approximately 50% of the fungaemic episodes were caused by other *Candida* species [8-10]. Patients with *C. albicans* sepsis often have other co-existing viral and bacterial infections and septic thrombophlebitis and have a significantly greater overall response to antifungal therapy and to the treatment given for the primary illness [8]. Non-albicans *Candida* species particularly *C. krusei* and *C. glabrata* have recently emerged as important causes of

candidaemia among neutropenic cancer or SCT patients who have received fluconazole prophylaxis [5,8,10,22]. They may be intrinsically resistant to fluconazole, but they are very susceptible to amphotericin-B and the new extended spectrum triazoles such as voriconazole and posaconazole [9,22,26]. The frequency of non-albicans *Candida* species as causes of bloodstream isolates and their susceptibilities to fluconazole, vary considerably among different countries worldwide [8,17,26,27]. Fungaemia, due to these organisms, carries high mortality rates in immunocompromised individuals, especially in patients with leukaemia, solid tumors and hepatic disorders [8,15,17,21,26,27]. As with reports of increased prevalence of non-albicans species of *Candida* in neutropenic patients, our study showed predominance of non-albicans species particularly *C. krusei* and *C. tropicalis*.

Over the past two decades, there has been a gradual increase in the number of patients with malignant haematological disorders at risk of invasive fungal infections [8,28,29]. Although CDC is a life threatening complication in immunocompromised individuals, the mortality rates due to CDC

are less than that encountered in candidaemia and invasive aspergillosis [18,28]. Only one fifth of the cases of CDC have positive blood cultures due to previous exposure to antifungal therapy or prophylaxis [23]. Studies have shown that the liver, the spleen, the lungs and the kidneys are the most frequently involved body organs [18]. Our study showed that disseminated *Candida* infections were seen more frequently with *C. albicans* and that the liver, the spleen and the kidneys were the most commonly involved body sites.

In many laboratories, the susceptibility testing of fungi is not considered a routine testing procedure [16]. It is most helpful in dealing with severe and invasive fungal infections due to non-albicans species of *Candida* [9,10,16]. Especially in patients treated with azole antifungal agents, the possibility of microbiological resistance should be taken into consideration [9-11,16,26,27]. Azole resistance for *C. albicans* has been reported in patients with HIV infection and in patients with invasive candidiasis [9-11,16].

Despite its adverse effects, conventional amphotericin-B has been the standard agent for the

treatment of invasive candidiasis [5,10,16]. Amphotericin-B related nephrotoxicity and other side effects have been associated with increased mortality, thus making the various lipid formulations of amphotericin-B more appropriate alternatives [16]. Most *Candida* isolates appear to remain susceptible to amphotericin-B although recent data indicate that *C. krusei* and *C. glabrata* may require relatively high doses of amphotericin-B [10,16]. In patients with febrile neutropenia, amBisome has comparable efficacy to conventional amphotericin-B and is associated with fewer breakthrough fungal infections and less nephrotoxicity and other side effects [30]. Caspofungin is as effective as amphotericin-B in the treatment of candidaemia and invasive *Candida* infections [31]. Flucytosine is active against many *Candida* isolates but its adverse effects have limited its use [16]. Despite the recent advances in antifungal therapy, intense efforts are still required to develop more effective antifungal agents for use in the treatment of severe and invasive fungal infections [32]. The late introduction of the new antifungal agents (voriconazole and caspofungin) at our institution and the avoidance of flucytosine use due to its myelotoxicity made

various amphotericin-B formulations the cornerstone of therapy for the candidaemic episodes discussed.

In patients with fungaemia, poor prognosis and high mortality rates are associated with: severe underlying illness, old age, prolonged neutropenia, culture of non-albicans species of *Candida*, septic shock, visceral dissemination and lack of antifungal prophylaxis [2,15,33]. The early recognition of candidaemia, the prompt removal of central venous catheters and the early initiation of an appropriate antifungal therapy improve the outcome of patients with candidaemia [15,34]. In our group of patients: prolonged neutropenia, untreated or relapsing primary disease, septic shock and the presence of non-albicans fungaemia were the leading causes of unsuccessful outcome.

## CONCLUSION

Candidaemia is an important cause of morbidity and mortality in patients with malignant haematological disorders and SCT. The use of fluconazole prophylaxis in neutropenic immunocompromised individuals is associated with the emergence of non-albicans species of *Candida*. Suc-



successful outcome of candidaemia depends upon the early administration of appropriate antifungal therapy and the early removal of infected intravascular devices, while the delayed recovery of neutropenia and the culture of non-albicans species of *Candida* are associated with poor prognosis. In patients with candidaemia, it is mandatory to perform repeated and thorough clinical assessment and to repeat appropriate serological and radiological investigations to rule out the possibility of disseminated candidiasis.

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