ORIGINAL ARTICLE

Epidemiology and outcome of *Candida* bloodstream infection in an intensive care unit in Hong Kong

CME

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Objective To study the epidemiology of *Candida* bloodstream infection in the Intensive Care Unit.

Design Retrospective study.

Setting A 22-bed, mixed medical and surgical Intensive Care Unit of a 1400-bed university teaching hospital in Hong Kong.

Patients All adult patients (>18 years) who had at least one blood culture positive for *Candida*.

Results During the 9 years of the study period, there were 128 patients with episodes of candidaemia (point prevalence, 9.6 per 1000 Intensive Care Unit admissions), 72 entailed albicans candidaemia and 56 non-albicans candidaemia. Albicans was still the predominant species, but the incidence of tropicalis was increasing. The median lengths of hospital and Intensive Care Unit stays prior to taking of the culture revealing candidaemia were 15 and 6 days, respectively. In all, 61% of patients did not have *Candida* colonisation within 2 weeks of their candidaemia. The main anti-fungal agents used were fluconazole and amphotericin B, but only 89 (70%) of the patients received appropriate anti-fungal treatment. Intensive Care Unit and hospital mortalities were 70% and 78%, respectively. Patients who did not receive appropriate treatment within 3 days had a worse outcome than those who did.

Conclusions Our data showed a high point prevalence of candidaemia in the Intensive Care Unit. Albicans was still the predominant species. Candidaemia occurred early during Intensive Care Unit stay, and a significant proportion of patients did not have prior fungal colonisation. Candidaemia in the Intensive Care Unit was associated with high morbidity and mortality. Many patients did not receive appropriately early anti-fungal therapy, and endured higher mortality than in the remainder.

Key words
Angifungal agent; *Candida albicans*; Candidiasis; Intensive care units; Survival rate

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Introduction

Invasive fungal infection is becoming increasingly important in critically ill patients, and *Candida* has become the fourth most common organism responsible for bloodstream infection in the intensive care unit (ICU).[1,2] There has also been an epidemiological shift to non-albicans species, which is most marked in immunocompromised patients. One reason for this shift was that in the 1980s, triazole-based anti-fungal chemoprophylaxis was commonly used together with empirical treatment of presumed *Candida* infections.[1-3] However, in most critically ill non-neutropenic patients, albicans still seems to be the predominant species.[1] Risk factors for invasive candidiasis in the ICU have been extensively studied. They include: prolonged ICU stays, *Candida* colonisation at multiple sites, severe illness, diabetes, renal failure, haemodialysis, receipt of broad-spectrum antibiotics, central venous catheterization, parenteral nutrition, immunosuppressive drugs, cancer, severe acute pancreatitis, surgery, and transplantation.[1,2,4-11] Nosocomial candidaemia is associated with high crude and attributable mortality rates,[2,10,12] and early effective therapy is important for improving outcomes.[2]

Candidaemia poses a challenge for ICU clinicians and it is often necessary to rely on epidemiological clues to entertain the diagnosis and initiate empirical treatment (based on the likely infective species). The frequency with which various *Candida* species are isolated in the ICU may differ significantly in different parts of the world. A number of epidemiological studies have examined candidaemia in adult ICUs, mainly in North

香港一所深切治療室內病人血液感染念珠菌的流行病學及結果

目的 探討深切治療室內病人血液感染念珠菌的流行病學。

設計 回顧研究。

安排 香港一所有1400張病床的大學教學醫院內，共有22張病床的外科及內科深切治療室。

患者 念珠菌血液測試呈陽性的所有18歲以上的病人。

結果 在9年的研究期間，共有128宗念珠菌血症（時點患病率：每1000位入住深切治療室病人中的9.6位），其中72宗屬白色念珠菌，另56宗屬非白色念珠菌。雖然白色念珠菌仍佔大多數，但熱帶假絲酵母菌有上升的趨勢。在進行念珠菌培養前，病人的住院和入住深切治療室時間的中位數分別為15天及6天。在出現念珠菌血症的兩個星期之間，61%病人未有念珠菌定植。主要用作治療的抗真菌藥有氟康唑和兩性霉素，但只有89名病人（70%）接受適當的抗真菌藥物治療。深切治療室死亡率為70%，住院死亡率為78%。病人如果不能於病發3天內得到適當的治療，會有較差的治療結果。

結論 本研究顯示，深切治療室病人對念珠菌血症出現高時點患病率。白色念珠菌仍佔大多數。念珠菌血症會在病人逗留深切治療室的早期出現，而大部份病人在此之前並未有念珠菌定植。深切治療室出現的念珠菌血症個案有高病發率和死亡率。很多病人因不能在病發早期得到適當的治療，以致有較高死亡率。

America, Europe, and Israel.[13-20] We therefore carried out a 9-year retrospective study for our ICU, to assess the incidence, epidemiology, and outcome of *Candida* bloodstream infections.

Methods

Study design

This was a retrospective study of *Candida* bloodstream infection in the ICU of a 1400-bed university teaching hospital in Hong Kong. The study period was from January 1998 to December 2006. The ICU was a mixed medical and surgical unit of 22 beds, with about 1300 admissions per year. We identified all adult patients (aged >18 years) who had at least one blood culture positive for *Candida*. Our hospital employs the BactT/ALERT (Biomerieux, US) as the blood culturing system. For the same ICU admission, duplicate or triplicate candidaemia events were only counted once. If a patient developed a second episode of candidaemia, this event would not be counted. Patients with *Candida* bloodstream infections were divided into two groups: those infected with *Candida albicans* and those infected with non-albicans species. Subjects who were infected with both albicans and non-albicans isolates were analysed as having non-albicans infections. The date of candidaemia was defined as the earliest date of sampling yielding a positive blood culture. The hospital case notes were reviewed by three clinicians, and demographic and clinical data were collected. Microbiological and laboratory data of each patient were retrieved from the computerised hospital database. Data on the total amount of antimicrobial use in the ICU were obtained from the Hospital Pharmacy. For the purpose of analysis, grams of antimicrobial agents used each year were converted into number of defined daily doses (DDDs),[21,22] and then expressed per 1000 patient days.

Data collection

For each ICU patient with candidaemia, demographic data, duration of hospital and ICU stays prior to the sampling that confirmed candidaemia, underlying disease states, factors related to the index hospitalisation, and outcomes were collected. Underlying disease states and factors of interest related to the index admission are listed in Table 1. *Candida* colonisation was defined as isolation of *Candida* from any body site or specimen (sputum or tracheal aspirate, urine, intravascular device, skin, stool, wound swabs, pus before the date of the candidaemia). These specimens could be taken as part of the sepsis workup or part of surveillance cultures. Severity of illness was compared using the APACHE (acute physiology and chronic health evaluation) II score.[23] Data on patient outcomes included: ICU mortality, hospital mortality, and length of ICU and hospital stays. The number of patients with episodes of candidaemia from 1998 to 2006 was expressed per 1000 patient admissions as well as per 10 000 ICU patient-bed days. The actual numbers of ICU admissions per year and ICU patient-days per year were retrieved from hospital admissions and discharge records. Use of antibiotics (including fluconazole) for all patients admitted to the ICU was also retrieved.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 10.0; SPSS Inc, Chicago [IL], US). Continuous variables were compared using Student's *t* test or the Mann-Whitney test. Categorical variables were compared using Chi squared or Fisher's exact tests. The Chi squared test for trend was performed to assess trend over time. A P value (2-tailed) of less than 0.05 was considered significant.

Results

Demographic data

During the 9 years of the study period (January 1998

TABLE 1. Patient demographics and underlying medical conditions*

Demographics and medical conditions†	Total episodes of candidaemia (n=128)	*Candida albicans* candidaemia (n=72)	Non-albicans candidaemia (n=56)	P value‡
Sex (M:F)	81:47	52:20	29:27	0.014
Age (years)	54 (43-68)	55 (44-71)	54 (42-64)	0.200
Hospital stay before candidaemia (days)	15 (7-26)	15 (6-26)	15 (9-26)	0.546
ICU stay before candidaemia (days)	6 (1-13)	6 (0-13)	6 (1-13)	0.990
APACHE II score	25 (18-31)	26 (18-31)	24 (19-31)	0.395
Diabetes mellitus	19 (15%)	15	4	0.044
Solid neoplasm	8 (6%)	4	4	0.729
Haematological neoplasm	17 (13%)	5	12	0.020
Chronic liver disease	18 (14%)	11	7	0.799
Chronic renal failure	15 (12%)	11	4	0.178
Transplant recipient	7 (5%)	3	4	0.804
Surgery	56 (44%)	33	23	0.720
Abdominal surgery	20 (16%)	12	8	0.809
Trauma	7 (5%)	5	2	0.467
Burns	8 (6%)	6	2	0.464
Neutropenia (<500 cells/mL)	14 (11%)	4	10	0.043
Acute renal failure	58 (45%)	37	21	0.152
Steroids	12 (9%)	7	5	1.000
Parenteral nutrition	24 (19%)	16	8	0.172
Antibiotics§	126 (98%)	70	56	0.252
Fluconazole use‖	13 (10%)	3	10	0.016
Fungal colonisation within 2 weeks of candidaemia	50 (39%)	26	24	0.469

* Data are shown in No., No. (%), or median (interquartile range)
† ICU denotes Intensive Care Unit, and APACHE acute physiology and chronic health evaluation
‡ P value compares albicans and non-albicans groups
§ Antibiotics: used for more than 48 hours during that hospital admission before candidaemia
‖ Fluconazole: used for more than 48 hours in the preceding 3 months

to December 2006), there were 128 patients with episodes of candidaemia. The point prevalence of patients with candidaemia in the ICU was 9.6 per 1000 patient admissions (95% confidence interval [CI], 8.1-11.4) which amounted to 22 per 10 000 patient-days (95% CI, 18.5-26.1). Among the 128 patients with episodes of candidaemia, 72 entailed albicans and 56 did not. The demographic data of these patients are summarised in Table 1. There were more males than females in the albicans group. The median length of hospital stay prior to the sampling that revealed candidaemia was 15 days, and the corresponding median length of ICU stay was 6 days (Table 1). More than half of the candidaemias occurred within the first week of ICU admission (Fig 1). As shown in Table 1, the majority of patients (61%) did not have fungal colonisation within 2 weeks of their candidaemia. In diabetic patients, albicans candidaemia occurred more frequently than the non-albicans type. However, in neutropenic patients, those with haematological malignancies, and those previously exposed to fluconazole, non-albicans candidaemia occurred more frequently; *Candida tropicalis* being the predominant species. In the two former groups, there were similar or overlapping types of patients.

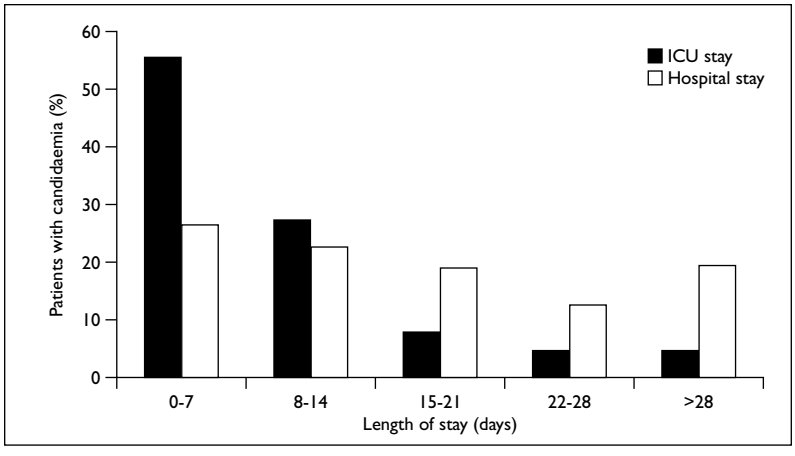

FIG 1. Time to onset of candidaemia from hospital and Intensive Care Unit (ICU) admission

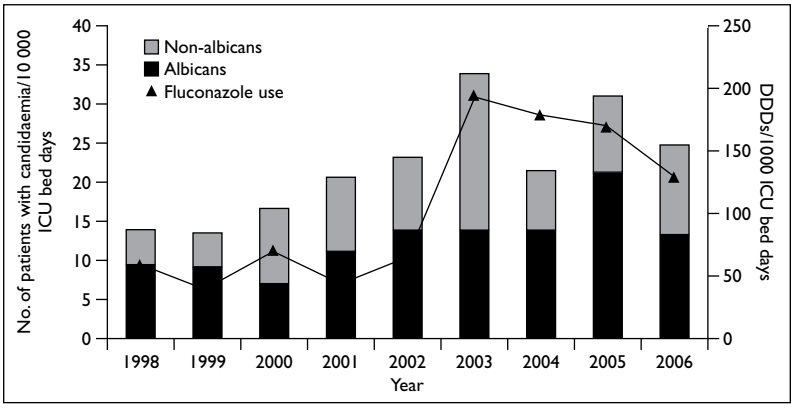

FIG 2. Candidaemia and antibiotic usage in the Intensive Care Unit (ICU) over time
Defined daily dose (DDD) of antimicrobial agent is calculated by dividing the total grams of the antimicrobial agent used by the number of grams in a daily average adult dose (the average adult daily dose of fluconazole assumed 400 mg/day)

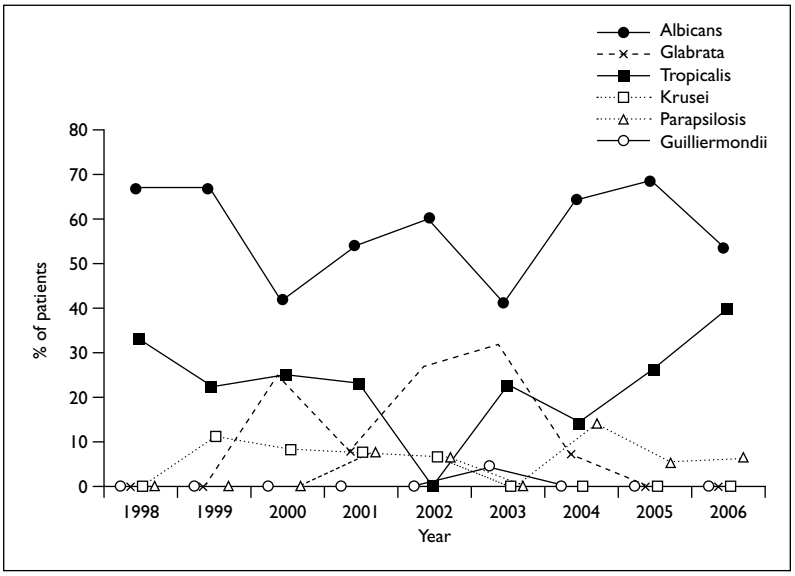

FIG 3. Species responsible for candidaemia isolated over time

None of the patients in our cohort was infected with the human immunodeficiency virus.

Incidence and species of candidaemia over time

Figure 2 reveals that there was a significant increase in the cumulative incidence of candidaemia over time from 1998 to 2003 (P=0.003), after which the rate stabilised. Six different species of *Candida* infecting the bloodstream were identified. *Candida albicans* was the commonest, accounting for 72 (56%) of the 128 patients. The other species were: *C tropicalis* (23%), *Candida glabrata* (13%), *Candida parapsilosis* (5%), *Candida krusei* (3%), and *Candida guilliermondii* (1%). The distribution of these species over time is shown in Figure 3.

The total antibiotic consumption per 1000 patient-days in the ICU increased steadily from 1350 DDDs in 1998 to 1750 in 2006. The total amount of fluconazole use increased markedly in year 2003 (Fig 2).

Treatment

The main anti-fungal agents used were fluconazole and amphotericin B deoxycholate; 36 patients having episodes of candidaemia were treated with amphotericin B only, and 35 with fluconazole only. Sequential treatment with amphotericin B followed by fluconazole or vice versa was used in 12 patients, and nine patients received either caspofungin or voriconazole. Thirty-six (28%) of the patients did not receive any anti-fungal treatment, of whom 35 died (33 within 3 days of the candidaemia). Three patients with *C glabrata* or *C krusei* bloodstream infection received inappropriate therapy with fluconazole, all of whom died in the ICU. Among those 89 patients who received appropriate anti-fungal treatment, the median (interquartile range) time interval between blood sampling and starting treatment was 2 (1-3) days.

Outcome

Table 2 shows the outcome of patients with candidaemia. Overall, ICU mortality was 70% and hospital mortality was 78%. The median lengths of ICU and hospital stays were 14 days and 28 days,

TABLE 2. Outcomes in patients with candidaemia*

Outcome†	Total episodes of candidaemias (n=128)	*Candida albicans* candidaemia (n=72)	Non-albicans candidaemia (n=56)	P value‡
Length of hospital stay (days)	28 (17-54)	32 (17-63)	24 (18-49)	0.370
Length of ICU stay (days)	14 (5-23)	14 (5-23)	14 (5-25)	0.778
ICU mortality	89 (70)	45 (63%)	44 (79%)	0.056
Hospital mortality	100 (78)	52 (72%)	48 (86%)	0.067

* Data are shown in No. (%) or median (interquartile range)
† ICU denotes Intensive Care Unit
‡ P value refers to difference between albicans and non-albicans groups

respectively. Among these 128 patients, 52 of the 72 patients with albicans candidaemia died, which gives a hospital mortality of 72%. Hospital mortality rates among patients with candidaemias due to glabrata (n=16), tropicalis (n=29), krusei (n=4), parapsilosis (n=6) and guilliermondii species (n=1) were 94%, 83%, 100%, 67%, and 100%, respectively. Since patients with non-albicans infections had significantly more haematological neoplasms, neutropenia, and fluconazole exposure, Chi squared tests were performed to assess whether there was an association between hospital mortality and the above-mentioned risk factors, but no significant association was noted. Figure 4 shows the relationship between the interval before starting therapy and mortality. Patients who received no treatment or inappropriate treatment, and patients who began treatment after 3 days of candidaemia, had worse outcomes than those who started appropriate therapy early.

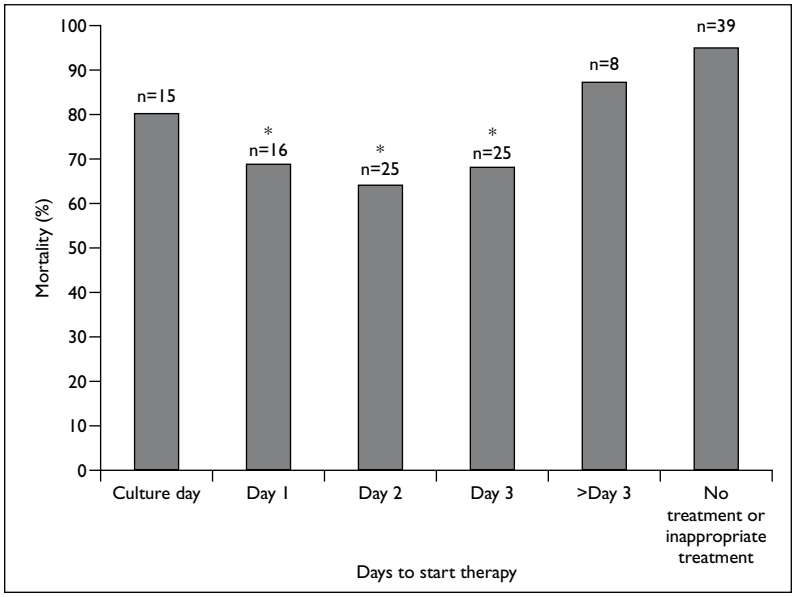

FIG 4. Relation of mortality and the time to start therapy
* P<0.05 vs no treatment or inappropriate treatment group

Discussion

Our data from 1998 to 2006 revealed that the point prevalence of candidaemia (9.6 patients per 1000 ICU patient admissions, which corresponds to 22 per 10 000 patient-days) was higher than that reported in most European, North American, and Israeli ICU cohorts (1.1 to 9.8 per 1000 patient admissions, 2.8 to 22 per 10 000 patient-days),[4,13,15-20,24] but less than that reported from Taiwan.[25] Whether this difference represents a genuine geographical difference or a difference in case mix is unclear. Many institutions reported an increase from 1980 to 1990, which then stabilised during the 1990s.[1,26] Our data also showed an increasing proportion of patients of ICU admissions having candidaemia from 1998 to 2003, after which it too stabilised. The year 2003 is notable for the severe acute respiratory syndrome (SARS) epidemic, which occurred in the months of March to May. Among the 22 patients with candidaemia in 2003, three had SARS. After that epidemic, increased resources were deployed on infection control and hospital antibiotic stewardship, which might have curbed further increases in the numbers of patients with candidaemia. Antibiotic use is believed to be a major risk factor predisposing to invasive candidiasis, yet the patient numbers with candidaemia did not parallel antibiotic usage in our ICU. On the other hand, fluconazole use followed a similar trend to the candidaemia infection rate, suggesting that *Candida* infection contributed to the increased ICU use of this drug.

Albicans was the predominant species causing candidaemia in our ICU. Among the non-albicans candidaemias, tropicalis was the major cause, followed by glabrata, parapsilosis, krusei, and guilliermondii. *Candida glabrata* and *C krusei* are resistant to fluconazole and *C guilliermondii* is intrinsically resistant to amphotericin B. It is therefore interesting that tropicalis candidaemias have increased since 2003, whereas infections due to all other non-albicans species revealed a decreasing trend. Our data showed that diabetes mellitus is a risk factor for albicans candidaemia, whereas non-albicans candidaemias were associated with exposure to fluconazole, neutropenia and haematological malignancy. However, these three risk factors may be co-associated and occur in patients in whom they overlap. Previous reports also showed an association between leukaemia and *C tropicalis* infection.[27,28] However, recent studies suggest that clinical features did not facilitate accurate differentiation of albicans from non-albicans candidaemia.[29,30]

Our data showed that invasive candidaemia occurred early during the ICU stay, mostly within the first week (Fig 1), probably reflecting the critical status of such patients. The second peak occurred during the second week, and was likely due to infection within the ICU. This is contrary to the belief that the single most important risk factor for invasive candidiasis was prolonged stay in the ICU.[11] Most studies have shown that the incidence of invasive candidiasis in the ICU peaks around day 10, and that the incidence of both *Candida* colonisation and invasive disease increases after day 8.[7,31-33] This difference may have been a consequence of case mix and epidemiology in our setting, as well as ICU bed availability and admission policies. We believe that a significant proportion of the patients with early candidaemia may have acquired the infection in the general wards, before admission to the ICU. Thus, it is important to consider this possibility for *Candida*

infections ensuing early in critically ill patients, as time spent in the ICU may not be crucial.

In line with past studies of candidaemia, previously identified risk factors were relatively frequent in our cohort. However, the majority of patients (61%) did not have documented antecedent *Candida* colonisation, which is actually a controversial risk factor. Whilst many authors have shown that it may be related to invasive candidaemia,[1,2] others have failed to demonstrate a clear association.[4,9] Current Infectious Diseases Society of America guidelines recommend empirical therapy for febrile non-neutropenic patients suspected of having disseminated candidiasis, only if there is evidence of colonisation with *Candida*, together with multiple risk factors for disseminated candidiasis and in the absence of any correctable cause.[34] The guidelines state that the absence of prior colonisation indicates a lower risk of invasive candidiasis and warrants delaying empirical therapy. Data from our cohort showed that in some ICU patients, strict adherence to these guidelines might delay empirical treatment.

In our cohort, the mainstay of treatment was fluconazole and amphotericin B deoxycholate. However, a significant proportion of patients did not receive appropriately early anti-fungal therapy; only 15 received such therapy within 24 hours, and a large proportion (28%) did not receive any treatment. Of the patients not treated with anti-fungal therapy, all but one died within 3 days of the index blood culture (ie before the results were available). The one survivor was a patient with an acute stroke and minor burns who had *Candida* isolated from burns wound, the central venous catheter, and the blood. The burns wounds were debrided and the central venous catheter removed, and the patient was discharged to the ward, before the blood culture results were known. The latter case illustrates the importance of source control, though pharmacological treatment is nevertheless warranted in all cases.

Previous studies have reported a crude mortality of 48 to 85% in ICU patients with candidaemia.[13,14,16,17,20] Prognostic factors for poor outcomes have included: old age, failure to remove central lines, malnutrition, neutropenia, and delayed treatment.[1,14] The crude hospital mortality in our series was high (78%) and likely to be due in part, to the failure to diagnose and treat a significant number of cases sufficiently early. Mortality rates are reported to vary according to the type of *Candida* species. In our cohort, hospital mortality rates for albicans, glabrata, tropicalis, krusei, parapsilosis and guilliermondii species were all high. It is not clear whether the higher observed mortality in non-albicans infections was related to the different species per se, or to disease/risk factors associated with their acquisition. In the literature, the outcome of candidaemias due to parapsilosis species has been reported to be better,[35] and worse with infections due to *C krusei* and *C glabrata*.[36-38] The mortality in our cohort showed such a trend, although there were no statistically significant differences. Previous studies have also shown that earlier therapy confers a better prognosis.[39,40] Garey et al[39] showed that the mortality rates in medical patients were lowest in those who began therapy on day 0 (being 15%), followed by those starting treatment on day 1 (mortality, 24%), day 2 (mortality, 37%), and day 3 or later (mortality, 41%). There was no such clear association in our cohort, which may be related to our ICU patients being more critical, as a significant number of the deaths were associated with, rather than attributable to, the candidaemia. However, patients who received no treatment or inappropriate treatment or started treatment after 3 days had worse outcomes than the others. Interestingly, patients who had early therapy (within 24 hours of positive culture) had a higher mortality (80%) than those who began therapy between days 1 and 3 (mortality, 67%), although this difference was not statistically significant (P=0.372). This observation is difficult to explain and may be a chance event due to the small number of our patients.

Our study was limited by being retrospective and it did not include controls. Also, a multivariate analysis to identify the risk factors for non-albicans infection and mortality would have been interesting, but was not permitted due to our small sample size. Nevertheless, our data do suggest that the epidemiology of our candidaemia may be different from that in North America and Europe.

In conclusion, we showed a higher point prevalence of ICU patients with candidaemia than in previously reported ICU cohorts. Albicans was still the predominant species, but tropicalis infections were becoming more frequent; both species remained fluconazole-sensitive. Candidaemia occurred early during ICU stay, and a significant proportion of the patients did not have prior colonisation. Candidaemia in the ICU was associated with high morbidity and mortality. Many patients did not receive appropriately early anti-fungal therapy, and in them mortality was higher.

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