Empirical treatment of candidemia in intensive care units: Fluconazole or broad-spectrum antifungal agents?

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The fear of candidemia caused by a fluconazole-resistant species of Candida is causing many intensive care units (ICUs) to switch empiric therapy from this drug to broad-spectrum antifungal agents. We studied the epidemiology and antifungal susceptibility of Candida isolates involved in cases of candidemia among adult and pediatric patients in ICUs from 1984 to 2006. We documented 307 episodes of candidemia in 307 patients, of which only eight episodes (2.6%) were caused by a fluconazole-resistant isolate. At least three of the eight patients from whom fluconazole-resistant strains were recovered had recently received fluconazole. Overall, only 1.6% of the episodes of candidemia caused by fluconazole-resistant strains (five patients) occurred in individuals with no evidence of previous fluconazole administration. In conclusion, the use of broad-spectrum antifungal agents is not justified in ICUs with a low proportion of candidemia episodes caused by fluconazole-resistant strains of Candida.

Keywords Candidemia, intensive care units (ICUs), Fluconazole resistance, empirical treatment

Introduction

The incidence of candidemia in population-based studies has been estimated to be between 1.7 and 10 episodes per 100,000 inhabitants per year [1–5]. A recent study carried out in Barcelona showed that around 33% of all episodes of candidemia occurred in patients in intensive care units (ICUs) [6]. Candidemia and invasive candidiasis have an attributable mortality close to 30% and can cause an increase in hospital spending to as much as $44,000 per episode [7,8].

Early and adequate antimicrobial therapy of candidemia is associated with a better outcome [9], but therapeutic efficacy depends on the underlying antifungal resistance of the Candida species that cause the infections. Candida albicans is still the main etiological agent of candidemia, but there has recently been a significant increase in the incidence of episodes caused by non-albicans Candida species, especially C. parapsilosis, C. tropicalis, C. glabrata, and C. krusei [10]. The fear of candidemia caused by fluconazole-resistant Candida species is a factor in the decision of many ICUs to switch empirical therapy from fluconazole to broad-spectrum antifungal agents such as amphotericin B or caspofungin.

Our hypothesis is that this change in the empirical therapeutic protocols may not be justified in many ICUs where candidemia caused by fluconazole-resistant strains is uncommon. Furthermore, fluconazole-resistance can be partially predicted on the basis of prior use of azoles. We assessed the incidence of fluconazole-resistant candidemia in the ICUs of our institution, particularly in patients with no previous history of fluconazole use.
Material and methods

Institutional information and microbiological procedures

Ours is a 1,750-bed tertiary teaching hospital serving a population of approximately 750,000 inhabitants in Madrid, Spain. It includes all medical and surgical specialties, in addition to pediatrics, psychiatry, obstetrics-gynecology, and oncology and two pediatric ICUs (pediatrics and neonatology). Samples were obtained when clinically indicated. Blood specimens were processed by means of the BACTEC-9240 system (Becton Dickinson, USA). The identification of the Candida species recovered from samples was based on the phenotypic features and their biochemical characteristics as determined through the use of CHROMagar and ID 32C (bioMérieux, Marcy-l’Etoile, France).

Patients and antifungal susceptibility testing

We retrospectively studied patients with candidemia admitted to our adult or pediatric ICUs or neonatology department from 1984 to 2006. We defined candidemia as the isolation of Candida spp. from 1 or more blood cultures. An episode of fungemia included all clinical isolates in the same admission.

Antifungal susceptibility testing was performed on all available isolates of Candida spp. (266 isolates) collected from blood samples. Fluconazole was obtained as reagent-grade powder from the manufacturer (Pfizer Pharmaceutical Group, New York, USA). The broth microdilution method was performed according to the CLSI M-27 A2 procedure (isolates recovered from 1984–2002) [11] and by means of a different broth microdilution method (Sensititre YeastOne; Trek Diagnostic Systems, Ltd., East Grinstead, UK) (isolates collected from 2003–2006) according to the manufacturer’s instructions. The inoculated microdilution trays were incubated at 35°C and read at 48 h. The MIC endpoint for fluconazole was defined as the lowest concentration producing a prominent inhibition of growth. The breakpoints of the CLSI M27-A2 protocol used to classify the isolates were as follows: susceptible = MIC = 8 μg/ml; susceptible-dose dependent, MIC = 16–32 μg/ml; and resistant = MIC = 64 μg/ml [11].

We selected for further study those patients from whom a fluconazole-resistant strain or a strain with diminished susceptibility to fluconazole was isolated (all isolates of C. krusei, C. glabrata, or other species with an MIC ≥ 64 μg/ml for fluconazole). The charts of these patients were reviewed and the following variables were recorded for each individual: clinical status, cause of admission to the ICU, risk factors for the development of candidemia, previous exposure to azoles during admission, antifungal treatment received, and outcome.

Results

During the study period (1984–2006), our laboratory detected 307 episodes of candidemia in 307 patients admitted to adult or pediatric ICUs. We found mixed fungemia in 4 patients (isolation of two different species of Candida in the same blood culture). The distribution of episodes by ICU was as follows: neonatology (128), general post-surgical (50), adult (76), major heart surgery (34), and pediatric (19).

Table 1 shows the distribution of Candida spp. isolated for blood samples. Overall, 283 (92.2%) of the episodes were caused by Candida spp. that are usually uniformly susceptible to fluconazole, i.e., C. albicans, C. tropicalis, C. parapsilosis, and a miscellany of other species. The remaining 24 episodes were due to either C. glabrata (19; 6.2%) or C. krusei (5; 1.6%).

A large proportion of episodes were caused by C. parapsilosis, but the distribution of this species was not homogeneous in all units; 98 (80.3%) episodes were found in the pediatric ICU, while the remainder (19.7%) occurred in the adult ICUs. Table 2 summarizes the clinical conditions of patients with candidemia caused by Candida isolates with diminished susceptibility to fluconazole (C. glabrata) and by strains that were resistant in vitro (C. krusei and other isolates with MICs ≥ 64 μg/ml) to this antifungal. The clinical chart of one of these 24 patients was not available.

Of these patients, eight did not survive long enough to receive antifungal treatment, six received amphotericin B, three received fluconazole, one caspofungin, two fluconazole followed by one fluconazole + amphotericin B, one amphotericin B followed by fluconazole,

### Table 1 Distribution by species of Candida isolates from the blood of patients admitted to ICU units. Number of episodes of candidemia caused per different Candida species and proportion of episodes caused by in vitro fluconazole-resistant strains.

<table>
<thead>
<tr>
<th>Species of Candida</th>
<th>Number of episodes of candidemia</th>
<th>Proportion of episodes caused by fluconazole-resistant strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>135 (43.9%)</td>
<td>0%</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>122 (39.7%)</td>
<td>0%</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>19 (6.2%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>17 (5.5%)</td>
<td>0%</td>
</tr>
<tr>
<td>Candida spp.¹</td>
<td>9 (2.9%)</td>
<td>0%</td>
</tr>
<tr>
<td>C. krusei</td>
<td>5 (1.6%)</td>
<td>5 (1.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>307 (100%)</td>
<td>8 (2.6%)</td>
</tr>
</tbody>
</table>

¹These strains were not available. Re-identification with chromogenic and ID 32C yeast identification systems was not possible.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Species of Candida</th>
<th>Fluconazole MIC (µg/ml)</th>
<th>ICU unit</th>
<th>Data of sample</th>
<th>Cause of admission in Intensive Care Unit</th>
<th>Other risk factors</th>
<th>Source of candidemia</th>
<th>Previous treatment with fluconazole</th>
<th>Treatment of the episode</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>C. glabrata</em></td>
<td>NA³</td>
<td>MHSPSU ²</td>
<td>23 February 1988</td>
<td>Major heart surgery</td>
<td>Unknown</td>
<td>No</td>
<td>None</td>
<td>Multi-factorial death</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><em>C. krusei</em></td>
<td>32</td>
<td>GPSU ⁴</td>
<td>23 October 1992</td>
<td>Liver &amp; transplantation</td>
<td>Unknown</td>
<td>No</td>
<td>Amphotericin B</td>
<td>Attributable death</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><em>C. glabrata</em></td>
<td>8</td>
<td>MHSPSU ⁴</td>
<td>13 September 1994</td>
<td>Major heart surgery</td>
<td>Unknown</td>
<td>No</td>
<td>Amphotericin B</td>
<td>Attributable death</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><em>C. glabrata</em></td>
<td>16</td>
<td>MICU ⁹</td>
<td>4 May 1995</td>
<td>Acute Ictus</td>
<td>Unknown</td>
<td>No</td>
<td>None</td>
<td>Multi-factorial death</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><em>C. glabrata</em></td>
<td>16</td>
<td>MICU</td>
<td>11 September 1995</td>
<td>Chronic Cardiac Congestion</td>
<td>Unknown</td>
<td>No</td>
<td>Removal of CVC</td>
<td>Multi-factorial death</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><em>C. glabrata</em></td>
<td>8</td>
<td>MICU</td>
<td>27 April 1996</td>
<td>COPD exacerbation</td>
<td>Unknown</td>
<td>No</td>
<td>Fluconazole (200 mG/day)</td>
<td>Improvement</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><em>C. krusei</em></td>
<td>64</td>
<td>MICU</td>
<td>30 August 1996</td>
<td>Chronic lymphocytic leukemia</td>
<td>Unknown</td>
<td>Yes¹⁰</td>
<td>Amphotericin B</td>
<td>Attributable death</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><em>C. glabrata</em></td>
<td>16</td>
<td>MHSPSU</td>
<td>3 September 1997</td>
<td>Mediastinitis after heart surgery</td>
<td>Unknown</td>
<td>No</td>
<td>None</td>
<td>Death during surgery</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><em>C. glabrata</em></td>
<td>16</td>
<td>GPSU</td>
<td>10 March 1998</td>
<td>Hepatopathy and ascites</td>
<td>Unknown</td>
<td>Yes</td>
<td>Removal of CVC</td>
<td>attributable death</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><em>C. glabrata</em></td>
<td>8</td>
<td>GPSU</td>
<td>15 February 1999</td>
<td>Peritonitis</td>
<td>CVC, ATB</td>
<td>Abdominal</td>
<td>CVC (400 mG/day) followed by fluconazole (400 mG/day)</td>
<td>Improvement</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><em>C. glabrata</em></td>
<td>4</td>
<td>MHSPSU</td>
<td>8 May 1999</td>
<td>Major heart surgery</td>
<td>CVC, ATB</td>
<td>Unknown</td>
<td>None</td>
<td>Attributable death</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td><em>C. glabrata</em></td>
<td>8</td>
<td>GPSU</td>
<td>25 October 2000</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td><em>C. glabrata</em></td>
<td>16</td>
<td>MICU</td>
<td>29 February 2000</td>
<td>Abdominal surgery</td>
<td>SURG, CORT, CVC, SUGR</td>
<td>Unknown</td>
<td>None</td>
<td>Multi-factorial death</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td><em>C. krusei</em></td>
<td>128</td>
<td>MICU</td>
<td>31 December 2002</td>
<td>Kidney transplantation</td>
<td>ATB, CORT, CVC</td>
<td>Abdominal</td>
<td>Fluconazole (400 mG/day) followed by Amphotericin B</td>
<td>Improvement</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><em>C. glabrata + C. albicans</em></td>
<td>16</td>
<td>MICU</td>
<td>17 April 2002</td>
<td>Surgery</td>
<td>SURG, Cancer, ATB, CVC, NTP</td>
<td>CVC</td>
<td>Yes (400 mG/day)</td>
<td>Attributable death</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td><em>C. glabrata</em></td>
<td>16</td>
<td>MHSPSU</td>
<td>18 July 2003</td>
<td>Acute myocardial infarction</td>
<td>ATB, CVC</td>
<td>Unknown</td>
<td>Fluconazole (400 mG/day) followed by Amphotericin B</td>
<td>Multi-factorial death</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td><em>C. glabrata</em></td>
<td>32</td>
<td>MHSPSU</td>
<td>19 August 2004</td>
<td>Major heart surgery</td>
<td>ATB, CVC</td>
<td>Unknown</td>
<td>Fluconazole (400 mG/day) followed by Amphotericin B</td>
<td>Multi-factorial death</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td><em>C. glabrata</em></td>
<td>32</td>
<td>NEOICU ¹¹</td>
<td>3 May 2004</td>
<td>Premature</td>
<td>ATB, CVC</td>
<td>Unknown</td>
<td>Removal of CVC</td>
<td>Improvement</td>
<td></td>
</tr>
</tbody>
</table>
and one caspofungin + amphotericin B. Outcome was favorable in 5 (21.7%) patients, whereas 6 (26.1%) died from candidemia, 2 (8.7%) during surgery, and 10 (43.5%) from different causes. The overall mortality of these patients was 78.3%.

However, only eight out of these 23 episodes (2.6% of the total number of episodes) were caused by an isolate that was intrinsically resistant or resistant in vitro to fluconazole (*C. krusei* or MIC ≥64 µg/ml). Four out of 5 (80%) patients with candidemia caused by *C. krusei* died. Of the 18 patients evaluated with candidemia caused by *C. glabrata*, 14 (77.8%) died. The in vitro classification of these isolates was as follows; susceptible (5 or 27.8%), susceptible dose-dependent (9 or 50%), resistant (3 or 16.7%) and data not available (1 or 5.5%). Three patients received fluconazole as monotherapy, one received the combination of fluconazole and amphotericin B, one received amphotericin B followed by fluconazole, and one patient received fluconazole followed by amphotericin B. Four of the isolates causing these episodes were susceptible dose-dependent and two were susceptible. Patients with susceptible dose-dependent isolates had a poor prognosis.

At least three of the eight patients from whom fluconazole-resistant strains were recovered had recently received fluconazole and/or suffered from hematological neoplasms. This means that only 5 (1.6%) of the episodes of candidemia caused by fluconazole-resistant strains occurred in patients who had not received fluconazole (Table 2). The outcome of these eight patients was poor, as six died even after antifungal therapy with antifungals other than fluconazole (in two patients, death was attributable to candidemia, whereas in four death was due to different causes).

In order to assess the evolution of fluconazole-resistant strains over time, we divided our study into three periods of approximately 8 years each and calculated the proportion of episodes of candidemia caused by real in vitro resistant strains, i.e., 1984–1991 (period 1, 0%), 1992–1999 (period 2, 2%), and 2000–2006 (period 3, 3.5%). Five of the 8 episodes caused by fluconazole-resistant strains occurred in 2006. Fig. 1 shows the proportion of episodes caused by each of the relevant *Candida* spp. in each study period. The susceptibility to fluconazole of isolates causing candidemia decreased from 1 µg/ml in period 1 to 2 µg/ml in period 2 and to 4 µg/ml in period 3.

### Discussion

Our data show that episodes of candidemia in the ICUs of our hospital are mainly caused by *Candida* spp. that...
are susceptible in vitro to fluconazole. If we focus only on microbiological data (low proportion of *Candida* isolates with diminished susceptibility to or even showing in vitro resistance), the widespread use of broad-spectrum antifungal agents for the empirical treatment of candidemia in our ICUs may not be justified.

A high proportion of episodes of candidemia in ICU patients occur in non-neutropenic hosts [6,12], and an increasing number of these episodes are now caused by non-*C. albicans* *Candida* isolates [6]. However, non-*C. albicans* *Candida* species are not necessarily resistant to fluconazole. In fact, *C. parapsilosis*, *C. tropicalis*, and many other species are almost uniformly susceptible to this antifungal. It is unusual to recover *C. albicans* isolates from blood that show in vitro resistance or reduced susceptibility to fluconazole and this species may be considered fluconazole-susceptible when involved in cases of candidemia [13–17].

Even in species that are resistant to fluconazole, such as *C. glabrata*, a high proportion of the isolates (>90%) have an in vitro MIC below 32 µg/ml [18]. Due to the limited data from cases of candidemia caused by fluconazole-resistant isolates of *C. glabrata*, it is difficult to formulate any conclusions on the use of this antifungal to treat invasive candidemia caused by isolates with MICs above 32 µg/ml [18–22]. In our opinion, patients with candidemia caused by *C. glabrata* should receive non-azole antifungal agents, e.g., echinocandins or amphotericin B. However, this does not infer that fluconazole as empirical treatment for invasive candidiasis would be ineffective for infections caused by *C. glabrata*. A retrospective study by Wilson *et al.* [19] showed that fluconazole was valuable in treating *C. glabrata* fungemia, with the elimination of the yeast from the bloodstream in 65% of their patients. It is also possible that the underlying conditions of these patients have a greater influence on prognosis than in vitro resistance of *C. glabrata* to fluconazole.

Guidelines from different societies and groups agree that broad-spectrum empirical coverage should be used with ICU patients with suspected invasive candidiasis, but the scientific basis for this recommendation is frequently weak, non-existent, or based on specific settings. IDSA guidelines for the treatment of invasive candidiasis recommend caspofungin or amphotericin B in cases of invasive candidiasis in unstable patients, while fluconazole should be employed for stable patients [23]. The definition of ‘unstable’ for ICU patients is imprecise, and often leads to massive use of broad-spectrum antifungal agents. In addition, the IDSA recommends (C-III) that patients with candidemia caused by *C. glabrata* be treated with high doses of fluconazole (800 mg/d).

The consequences of more widespread use of broad-spectrum antifungal agents in ICU patients have not been properly evaluated, but experience in hematology units shows that massive use of fluconazole caused a shift in the emergence of non-*C. albicans* *Candida* species in these units [3]. Another example of the consequences of the overuse of broad-spectrum antifungal agents can be found in the emergence of invasive mucormycosis in some hematology units after indiscriminate prophylaxis with voriconazole [24]. In comparison with amphotericin B or caspofungin, fluconazole is better tolerated and less expensive than either of these two drugs.

In our institution, the highest number of episodes of candidemia was recorded in 2006 but the reasons for this increased incidence remain unclear. Four of the 8 cases of candidemia caused by fluconazole-resistant strains occurred during 2006. The presence of a higher proportion of fluconazole-resistant strains should be carefully monitored in the future, and the trend in the isolation of these strains over periods longer than a single year should be assessed.

It is difficult to establish the proportion of isolates that are resistant in vitro to a specific antimicrobial agent that would justify a change in empirical therapy. We believe that the incidence of 2.16% *Candida* strains causing invasive candidiasis in our adult and pediatric ICUs were of fluconazole-resistant does not justify replacing fluconazole with extensive broad-spectrum antifungal treatment. Moreover, we detected recent administration of fluconazole in three of the eight patients with fluconazole-resistant strains. These patients should have received a different non-azole antifungal agent.

In conclusion, the use of broad-spectrum antifungal agents is not justified in ICUs with a low proportion of candidemia episodes caused by fluconazole-resistant strains of *Candida*. **Fig. 1** Distribution of the etiological agents of candidemia over the three parts of the study period, showing the proportion of episodes caused by each species of *Candida*. **Table 1** Distribution of the etiological agents of candidemia over the three parts of the study period, showing the proportion of episodes caused by each species of *Candida*. **Table 2** Distribution of the etiological agents of candidemia over the three parts of the study period, showing the proportion of episodes caused by each species of *Candida*.
Acknowledgements

We would like to thank Thomas O’Boyle for writing assistance during the preparation of this manuscript.

Disclosure of conflicts of interest

This study does not present any conflict of interest for its authors. This study was partially financed by grants from CIBER RES CD06/06/0058.

Jesús Guinea Pharm D, PhD is contracted by the Fondo de Investigación Sanitaria (FIS) CM05/00171.

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This paper was first published online on iFirst on 29 October 2008.