Candidaemia associated with decreased in vitro fluconazole susceptibility: is Candida speciation predictive of the susceptibility pattern?

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Background: Candidaemia is often treated with fluconazole in the absence of susceptibility testing. We examined factors associated with candidaemia caused by Candida isolates with reduced susceptibility to fluconazole.

Methods: We identified consecutive episodes of candidaemia at two hospitals from 2001 to 2007. Species identification followed CLSI methodology and fluconazole susceptibility was determined by Etest or broth microdilution. Susceptibility to fluconazole was defined as: full susceptibility (MIC ≤ 8 mg/L); and reduced susceptibility (MIC ≥ 32 mg/L). Complete resistance was defined as an MIC > 32 mg/L.

Results: Of 243 episodes of candidaemia, 190 (78%) were fully susceptible to fluconazole and 45 (19%) had reduced susceptibility (of which 27 were fully resistant). Of Candida krusei and Candida glabrata isolates, 100% and 51%, respectively, had reduced susceptibility. Despite the small proportion of Candida albicans (8%), Candida tropicalis (4%) and Candida parapsilosis (4%) with reduced fluconazole susceptibility, these species composed 36% of the reduced-susceptibility group and 48% of the fully resistant group. In multivariate analysis, independent factors associated with reduced fluconazole susceptibility included male sex [odds ratio (OR) 3.2, P = 0.01], chronic lung disease (OR 2.7, P = 0.01), the presence of a central vascular catheter (OR 4.0, P < 0.01) and prior exposure to antifungal agents (OR 2.2, P = 0.04).

Conclusions: A significant proportion of candidaemia with reduced fluconazole susceptibility may be caused by C. albicans, C. tropicalis and C. parapsilosis, species usually considered fully susceptible to fluconazole. Thus, identification of these species may not be predictive of fluconazole susceptibility. Other factors that are associated with reduced fluconazole susceptibility may help clinicians choose adequate empirical anti-Candida therapy.

Keywords: candidiasis, fungal infections, antifungals, antibiotic resistance

Introduction

Fluconazole is often used in the treatment of candidaemia and is recommended by the Infectious Diseases Society of America as first-line therapy for this condition.1 In many institutions, fluconazole is also used for the prevention of invasive Candida infections. Following its widespread use, several surveys of Candida susceptibility report the emergence of strains with reduced susceptibility as well as resistance to fluconazole.2–5 The use of fluconazole in patients infected with isolates with reduced fluconazole susceptibility may be inadequate and result in treatment failure.

Clinicians need guidance when choosing an appropriate anti-Candida agent for the treatment of invasive candidiasis, but in most hospitals Candida susceptibility testing is not routinely performed. As a result, clinicians often rely on the Candida species as a predictor of fluconazole susceptibility. Such a strategy is limited in several ways. Some species that are generally considered fully susceptible to fluconazole may include subpopulations with reduced susceptibility. On the other hand, many non-albicans Candida isolates remain fully susceptible to fluconazole. Of the non-albicans species, Candida krusei is the only one that is predictably fluconazole resistant. However, it remains a relatively uncommon species among patients...
M. Candida species are common causes of candidaemia, even a fluconazole reduced-susceptibility isolate. Factors that are associated with candidaemia involving a fluconazole reduced-susceptibility isolate.

Another strategy to improve anti-Candida treatment choices is to stratify patients according to their risk of having invasive candidiasis with a fluconazole reduced-susceptibility isolate. Such an approach would enable clinicians to begin effective antifungal therapy earlier, even before Candida species identification is available. Risk factors associated with reduced fluconazole susceptibility have not been studied. In this study, we sought to identify factors that are associated with candidaemia involving a fluconazole reduced-susceptibility isolate.

Methods

Study design and population

We performed a retrospective, case–comparator study at two tertiary care university hospitals in the Boston (MA, USA) area. We searched the microbiology laboratory logs to identify all consecutive patients with a Candida bloodstream infection, defined as the isolation of any species of Candida from at least one set of blood cultures, between the years 2001 and 2007 (Tufts Medical Center) and 2005 and 2006 (Brigham & Women’s Hospital). For patients with multiple candidaemia episodes, only the first episode was included. The study’s protocol was approved by the institutional review boards of both centres. The case group included all patients whose Candida isolate had reduced susceptibility to fluconazole. The comparator group included all patients with a fully susceptible isolate.

Data collection

Data sources included patient medical charts, microbiology logs and the hospitals’ informatics systems. Data were collected for the purpose of this study by trained study team members. Data collected included patient demographics, co-morbidities, pre-candidaemia surgeries, exposure to antibacterial, antifungal and immunosuppressant agents, central venous catheterization, receipt of total parenteral nutrition, dialysis or blood transfusions, use of mechanical ventilation, and infection or colonization with other selected organisms. Laboratory values collected included the presence or absence of leucocytosis, leucopenia, anaemia, liver function test abnormalities, reduced creatinine clearance, or coagulopathy. All data were collected into a pre-prepared Microsoft Excel data collection form.

Species identification and susceptibility testing

Candida species identification followed CLSI methodology. Fluconazole susceptibility testing was performed either by Etest or broth microdilution, according to CLSI guidelines. For broth microdilution, the microtitre plates were incubated at 35°C for 24–48 h. The amount of growth in the well containing the antifungal agent was compared with the amount of growth in an antifungal-free growth control well. The MIC was read as the lowest concentration of antifungal that inhibited 50% of growth of the organism, detected visually. Quality control was ensured by testing the CLSI recommended quality control strains: Candida parapsilosis ATCC 22019 (MIC range 2–8 mg/L); and C. krusei ATCC 6258 (MIC range 16–64 mg/L). All of the available isolates were also cross-tested at MD Anderson Medical Center mycology laboratory. Three susceptibility groups were defined: fully susceptible (MIC ≤ 8 mg/L); reduced susceptibility (MIC > 32 mg/L); and complete resistance (MIC > 32 mg/L).

Analysis

Our aim was to identify baseline and acquired characteristics of patients who developed candidaemia with isolates that had reduced susceptibility to fluconazole, as compared with patients who had candidaemia with isolates that were fully susceptible to fluconazole. Factors associated with candidaemia with reduced susceptibility to fluconazole were examined using χ² tests or univariate logistic regression. Variables that had significance at a P<0.1 level in the univariate analysis were considered candidates for the building of multivariate models. Stepwise and best subsets approaches were used to build multivariate logistic regression models, to determine which variables were most strongly associated with fluconazole reduced-susceptibility candidaemia as compared with fully fluconazole-susceptible candidaemia. The models contained variables that were a priori considered to be clinically relevant to avoid finding spurious associations. All statistical analyses were performed in SAS, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient population and Candida isolates

A total of 270 consecutive candidaemia episodes were identified, of which 243 isolates (90%) were available for susceptibility testing and were included in this study. Tufts Medical Center and Brigham & Women’s Hospital contributed 95 and 148 candidaemia episodes, respectively. The infecting Candida species included: C. albicans, 111 (46%); C. glabrata, 50 (21%); C. tropicalis, 28 (12%); C. parapsilosis, 39 (16%); C. krusei, 6 (2%); Candida lusitaniae, 4 (1.5%); Candida guilliermondii, 2 (0.5%); and other Candida spp., 3 (1%).

Overall fluconazole susceptibility

Of a total of 243 isolates, 190 (78%) were fully susceptible to fluconazole (MIC ≤ 8 mg/L), 8 (3%) had an MIC of 16 mg/L, 18 (7%) had an MIC of 32 mg/L and 27 (11%) were fluconazole resistant (MIC > 32 mg/L). A total of 45 isolates (19%) showed reduced susceptibility to fluconazole (MIC ≥ 32 mg/L). For the risk factor analysis, the case group included all 45 patients with a reduced-susceptibility Candida isolate and the comparator group included all 190 patients with a fully susceptible Candida isolate.

Fluconazole susceptibility within Candida species

Fluconazole susceptibility within Candida species is presented in Figure 1. C. krusei and C. glabrata showed the highest ratios of
fluconazole reduced susceptibility with 100% and 51% of isolates, respectively, showing reduced fluconazole susceptibility, and 83% and 18% of isolates, respectively, displaying complete fluconazole resistance. *C. albicans* showed the highest ratio of fluconazole susceptibility. A small proportion of *C. albicans* (8%), *C. tropicalis* (4%) and *C. parapsilosis* (4%) displayed reduced fluconazole susceptibility.

**Contribution of each Candida species to the fluconazole reduced-susceptibility group**

Figure 2 presents the distribution of fluconazole MICs in the entire study population, highlighting the relative contribution of each *Candida* species to each MIC level. While all *C. krusei* isolates had reduced fluconazole susceptibility, they comprised only 13% of the entire reduced-susceptibility group and 19% of the fully resistant group. *Candida* species that are generally considered to be fluconazole susceptible, including *C. albicans*, *C. tropicalis* and *C. parapsilosis*, comprised 36% of the entire reduced-susceptibility group and 48% of the fully resistant group (Figure 3).

**Factors associated with reduced fluconazole susceptibility**

Specific exposures and baseline patient characteristics, and their association with reduced fluconazole susceptibility are presented in Table 1. Patients with reduced-susceptibility isolates were more likely to be male (76% versus 53%, \(P<0.01\)), be located in the intensive care unit (ICU) pre-candidaemia (76% versus 49%, \(P<0.01\)) and have a longer pre-candidaemia hospital stay (24 versus 16 days, \(P=0.02\)). Patients with a reduced-susceptibility isolate were also more likely to have chronic lung disease (36% versus 16%, \(P<0.01\)), have been colonized or infected with vancomycin-resistant Enterococcus (VRE) (29% versus 12%, \(P<0.01\)), have a central vascular line (84% versus 54%, \(P<0.01\)), have been exposed to antifungals during the current hospital admission (47% versus 28%, \(P=0.01\)) and have been exposed to vancomycin during the current admission (84% versus 68%, \(P=0.03\)).

The results of the multivariate model are presented in Table 2. Patients with reduced-susceptibility isolates were more likely to be male [odds ratio (OR) 3.2, \(P<0.01\)], have chronic lung disease (OR 2.7, \(P=0.01\)), have a central vascular catheter...
and have been previously exposed to antifungal agents (OR 2.2, \( P = 0.04 \)).

**Discussion**

Previous studies that grouped candidaemia cases as either \( C. \) albicans or non-\( C. \) albicans did so because they were examining risk factors for infections with the potential to be less susceptible to fluconazole.\(^{15-18} \) In this study, we classified cases by fluconazole susceptibility, regardless of \( C. \) species. We were particularly interested in examining the distribution of \( C. \) species among patients with infections that had reduced fluconazole susceptibility and in identifying factors that are associated with reduced fluconazole

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### Table 1. Univariate analyses: patients' characteristics stratified by fluconazole susceptibility group

<table>
<thead>
<tr>
<th></th>
<th>All, ( n = 235 )</th>
<th>Fluconazole MIC ( \leq 8 ) mg/L, ( n = 190 )</th>
<th>Fluconazole MIC ( \geq 32 ) mg/L, ( n = 45 )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and hospitalization characteristics of patients with ( C. ) bloodstream infection by fluconazole MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, years (mean( \pm ) SD)</td>
<td>58 ( \pm ) 17</td>
<td>57 ( \pm ) 17</td>
<td>62 ( \pm ) 15</td>
<td>0.09</td>
</tr>
<tr>
<td>sex, male (%)</td>
<td>56</td>
<td>53</td>
<td>76</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>ICU admissions pre-candidaemia (%)</td>
<td>51</td>
<td>49</td>
<td>76</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>ICU days pre-candidaemia (mean( \pm ) SD)</td>
<td>7 ( \pm ) 16</td>
<td>6 ( \pm ) 14</td>
<td>13 ( \pm ) 24</td>
<td>0.03</td>
</tr>
<tr>
<td>hospital days pre-candidaemia (mean( \pm ) SD)</td>
<td>17 ( \pm ) 19</td>
<td>16 ( \pm ) 18</td>
<td>24 ( \pm ) 25</td>
<td>0.02</td>
</tr>
<tr>
<td>Co-morbidities and exposures of patients with ( C. ) bloodstream infection by fluconazole MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardiovascular disease (%)</td>
<td>49</td>
<td>47</td>
<td>56</td>
<td>0.29</td>
</tr>
<tr>
<td>chronic lung disease (%)</td>
<td>20</td>
<td>16</td>
<td>36</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>chronic renal dysfunction(^a) (%)</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>0.95</td>
</tr>
<tr>
<td>chronic haemodialysis (%)</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>0.27</td>
</tr>
<tr>
<td>liver cirrhosis (%)</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>0.27</td>
</tr>
<tr>
<td>solid organ malignancy (%)</td>
<td>26</td>
<td>26</td>
<td>29</td>
<td>0.67</td>
</tr>
<tr>
<td>haematological malignancy (%)</td>
<td>19</td>
<td>17</td>
<td>27</td>
<td>0.13</td>
</tr>
<tr>
<td>neutropenia (%)</td>
<td>16</td>
<td>16</td>
<td>18</td>
<td>0.71</td>
</tr>
<tr>
<td>immunosuppressed—any cause (%)</td>
<td>47</td>
<td>45</td>
<td>56</td>
<td>0.21</td>
</tr>
<tr>
<td>diabetes mellitus (%)</td>
<td>14</td>
<td>15</td>
<td>9</td>
<td>0.30</td>
</tr>
<tr>
<td>central vascular catheter (%)</td>
<td>75</td>
<td>54</td>
<td>84</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>total parenteral nutrition (%)</td>
<td>37</td>
<td>38</td>
<td>29</td>
<td>0.23</td>
</tr>
<tr>
<td>red blood cell transfusion (%)</td>
<td>65</td>
<td>63</td>
<td>73</td>
<td>0.20</td>
</tr>
<tr>
<td>mechanical ventilation (%)</td>
<td>39</td>
<td>39</td>
<td>40</td>
<td>0.92</td>
</tr>
<tr>
<td>anaemia (haemoglobin (&lt; 10 ) g/L) (%)</td>
<td>77</td>
<td>75</td>
<td>84</td>
<td>0.19</td>
</tr>
<tr>
<td>vancomycin-resistant ( E. ) (%)</td>
<td>16</td>
<td>12</td>
<td>29</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>vancomycin-resistant ( S. ) (%)</td>
<td>13</td>
<td>12</td>
<td>16</td>
<td>0.50</td>
</tr>
<tr>
<td>multiresistant Gram-negative(^b) (%)</td>
<td>16</td>
<td>14</td>
<td>24</td>
<td>0.09</td>
</tr>
<tr>
<td>steroid therapy (&gt;15 ( \mu )g/day) (%)</td>
<td>34</td>
<td>31</td>
<td>47</td>
<td>0.05</td>
</tr>
<tr>
<td>fluconazole exposure (%)</td>
<td>20</td>
<td>18</td>
<td>29</td>
<td>0.10</td>
</tr>
<tr>
<td>any antifungal exposure (%)</td>
<td>31</td>
<td>28</td>
<td>47</td>
<td>0.01</td>
</tr>
<tr>
<td>vancomycin exposure (%)</td>
<td>73</td>
<td>68</td>
<td>84</td>
<td>0.03</td>
</tr>
<tr>
<td>piperacillin/tazobactam exposure (%)</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>0.99</td>
</tr>
<tr>
<td>third-generation cephalosporin exposure (%)</td>
<td>45</td>
<td>43</td>
<td>53</td>
<td>0.19</td>
</tr>
<tr>
<td>any anti-anaerobic antibiotic exposure (%)</td>
<td>59</td>
<td>56</td>
<td>71</td>
<td>0.06</td>
</tr>
<tr>
<td>any antibiotic exposure (%)</td>
<td>87</td>
<td>87</td>
<td>89</td>
<td>0.71</td>
</tr>
</tbody>
</table>

\(^a\)Defined as a serum creatinine level \( > 1.5 \) mg/L.

\(^b\)Defined as the isolation of a Gram-negative bacteria with resistance to at least three antibiotic classes.

### Table 2. Multivariate analysis: independent factors associated with reduced fluconazole susceptibility among 235 consecutive patients with candidaemia

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio, MIC ( \geq 32 ) mg/L versus MIC ( \leq 8 ) mg/L</th>
<th>95% Confidence interval</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3.2</td>
<td>1.5–7.1</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>2.7</td>
<td>1.2–5.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Central vascular line</td>
<td>4.0</td>
<td>1.6–9.7</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>Antifungal exposure</td>
<td>2.2</td>
<td>1.1–4.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

\( OR 4.0, \( P < 0.01 \) \)
susceptibility. Such factors could help guide the choice of empirical anti-

Candida agents.

As expected, all C. krusei isolates were found to have reduced

fluconazole susceptibility. However, only 13% of those with

reduced susceptibility had an infection caused by C. krusei, con-

sistent with the relative rarity of this species among patients with

candidaemia. C. glabrata was the most common Candida species

among those with reduced fluconazole susceptibility (51%); how-

ever, 22 of 45 C. glabrata isolates (49%) remained fully sus-

ceptible to fluconazole. Perhaps the most important finding was

that 36% of those patients with a reduced-susceptibility organ-

ism and 48% of those with a fully resistant organism were

infected by C. albicans, C. tropicalis or C. parapsilosis, species gen-

erally considered to be fully fluconazole susceptible.

In multivariate analysis, two pre-existing conditions—male

gender and chronic lung disease—were strongly associated

with infections caused by reduced-susceptibility isolates.

Additionally, several acquired factors, including ICU admission,

longer hospital stay, the presence of a central vascular catheter,

recent receipt of antifungals or vancomycin and VRE coloniza-

tion, were also associated with reduced-susceptibility infections.

Although not previously studied in relation to fluconazole

reduced susceptibility, higher levels of healthcare and antibiotic

exposure have been associated with a higher risk of colonization

by antibiotic-resistant Gram-positive and Gram-negative bac-

teria.19 – 21 The reason for the association between male gender

and candidaemia caused by a non-albicans Candida organism

remains unclear. It may be related to differences in Candida colo-

nization patterns between men and women or hormonal effects

on fungal pathogenesis. While the presence of chronic lung

disease may have a direct impact on vulnerability to reduced-

susceptibility infections, it may also be an unmeasured confoun-

der. We found that prior antifungal exposure was associated with

reduced fluconazole susceptibility. Most of this exposure was to

fluconazole or another triazole. This association could be the

result of a selective pressure imposed by prior azole therapy. A

similar association was previously described for the isolation of

non-albicans Candida isolates.9,22 The association between VRE

colonization and reduced fluconazole susceptibility may be the

result of several factors. VRE colonization is usually a marker of

high-level exposure to healthcare and antibiotics.19,21 Among

persons who are already colonized with antibiotic-resistant bac-

teria, the increased risk of colonization or infection by other

resistant bacteria is well described. Our findings suggest that

such an association also exists for Candida. Candida, like VRE, fre-

quently colonizes the gut and is therefore exposed to a similar

antimicrobial-related selection pressure.

Our findings also suggest that the identification of a specific

Candida species should be used cautiously as the sole criterion

for anti-Candida agent choice. The only Candida species whose

identification reliably predicted reduced susceptibility was

C. krusei. The finding that infections caused by a reduced-

susceptibility organism were frequently caused by C. albicans,

C. tropicalis or C. parapsilosis questions the use of the identifi-

cation of these species as a definitive criteria for full susceptibility

and, therefore, the adequacy of lower-dose fluconazole use. In

our study, such a practice could have resulted in inappropriate

therapy and, possibly, treatment failure in approximately

one-third of reduced-susceptibility cases. On the other hand, in

our study, relying solely on the identification of non-albicans

Candida species alone to predict reduced fluconazole suscepti-

bility may have led clinicians to not use fluconazole in many cases

where it could be used successfully.

Rapid tests, such as fluorescent in situ hybridization, that

differentiate between C. albicans and C. non-albicans species

have been used to distinguish infections caused by fully suscep-

tible (C. albicans) and reduced-susceptibility (non-albicans)

organisms, and serve as guidance to clinicians.23,24 The use of

such tests alone in our cohort would have failed to predict the

level of fluconazole susceptibility at both ends of the prediction.

Our study has several strengths as well as limitations. To

prevent selection bias, we included all consecutive candidaemia

episodes in two centres. This resulted in a large and representa-

tive cohort of adult patients with candidaemia. However, the

number of patients with a reduced-susceptibility isolate was

limited. Nevertheless, we were able to explore the associations

with patient characteristics and identify several factors associ-

ated with reduced susceptibility. Our study was limited to two

tertiary care medical centres; therefore, as Candida species dis-

tribution as well as fluconazole susceptibility rates may vary signi-

ficantly from hospital to hospital, the generalizability of our

findings is limited. An additional limitation is the non-availability

of susceptibility testing of 27 of the 270 isolates (10%). While

possibly biasing our results, we could not identify any systematic

cause for the missing isolates and assume that the analysed

cohort is representative of the overall candidaemia population.

Determining fluconazole susceptibility, whether it is by broth

microdilution or Etest, is challenging. Results are sometimes dif-

ficult to interpret and are not always reproducible. We attempted

to control for this by sending all the available isolates for confir-

matory testing at another centre (MD Anderson) and also by

eliminating from the analysis those cases in which susceptibility

testing gave borderline results (e.g. isolates with a fluconazole

MIC of 16 mg/L).

In summary, we found that a significant number of episodes

of candidaemia with isolates that had reduced susceptibility to

fluconazole were caused by Candida species generally con-

sidered to be fully susceptible to fluconazole. Similarly, we found

that a large number of infections caused by isolates that were fully

susceptible to fluconazole were with species often considered to be

fluconazole resistant. We also found several risk factors associ-

ated with reduced susceptibility. Our study was limited to two

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that a large number of infections caused by isolates that were fully

susceptible to fluconazole were with species often considered to be

fluconazole resistant. We also found several risk factors associ-

ated with reduced-susceptibility infections. To further character-

ize bloodstream infections caused by Candida with reduced fluconazole

susceptibility and expand the generalizability of our study results to

various clinical settings, larger multicentre studies (including ter-

ciary care as well as primary care and long-term healthcare facili-

ties) are needed. Until data from such studies become available,

the results of our study may provide guidance to clinicians caring

for patients with candidaemia.

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Candidaemia and fluconazole susceptibility

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References