Incidence of candidaemia and relationship with fluconazole use in an intensive care unit

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Objectives: Candida spp. are the most important non-bacterial pathogens in critically ill patients. The aim of this study was to evaluate trends in the incidence of candidaemia and the distribution of Candida albicans and non-albicans over a 9 year period (1999–2007), and to assess their relationship with fluconazole use.

Methods: This was an interventional cross-over study. Patients admitted to the intensive care unit (ICU) who developed a clinically and microbiologically documented candidaemia were analysed. Fluconazole was used as prophylaxis in critically ill patients until 2002; from January 2003 infectious disease consultants strongly discouraged its use. Fluconazole use, measured as defined daily dose per 1000 patient-days, was calculated. The main outcome of the study is the evaluation of the restriction policy in terms of change in fluconazole use and in incidence of candidaemia.

Results: During the 108 month period (January 1999–December 2007), a total of 213 episodes of candidaemia (average incidence 1.42 episodes/10000 patient-days/year, range 0.36–3.02 episodes) were recorded in a mixed medical and surgical ICU in Italy. C. albicans was the most prevalent isolated species (n=98, 46%); non-albicans (n=115, 54%) were mainly represented by Candida parapsilosis (n=46, 22%) and by Candida glabrata (n=28, 13%). Segmented regression analysis of the interrupted time series showed that a change in the fluconazole prophylactic strategy resulted in a significant reduction in fluconazole use from the second semester of 2002. A dramatic decrease in the incidence of fungaemia due to C. non-albicans was observed from the second semester of 2003 (intervention effect in the second semester of 2007: −2.31/10000 patient-days); minor changes in the incidence of C. albicans fungaemia emerged (intervention effect in the second semester of 2007: −0.23/10000 patient-days).

Conclusions: The study showed a clear correlation between fluconazole use control and decreasing incidence of non-albicans candidaemia. Even if fluconazole remains a first-line treatment option in invasive candidiasis, its prophylactic use should be carefully evaluated.

Keywords: Candida, fungaemia, ICU

Introduction

Candida is an increasing cause of bloodstream infection, causing significant mortality and morbidity, especially in non-neutropenic critically ill patients. Its overall incidence has increased 5-fold in the past 10 years, and Candida spp. are currently between the fourth and the sixth most common nosocomial bloodstream isolate in the USA and in Europe.1,2 Despite the availability of

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effective antifungal therapy, mortality in the last decade has remained high, ranging from 36% to 63%. \textsuperscript{3} Candida albicans is responsible for the majority of Candida infections,\textsuperscript{2,4–6} but a substantial shift towards dose-dependent azole-susceptible, or even intrinsically azole-resistant, non-albicans Candida spp., e.g. Candida glabrata and Candida krusei, has been observed in some studies.\textsuperscript{7–11} An increasing role for non-albicans species was also noticed in studies performed among intensive care unit (ICU) patients, although the issue is somewhat controversial.\textsuperscript{1,12–14} Thus, despite a general trend towards increased rates of isolation of non-albicans Candida spp., the frequency of isolation and the relative proportion of C. albicans to non-albicans Candida spp. are highly divergent in different European countries and hospitals. Since 1990, fluconazole has been well established as a leading drug in the setting of prevention and treatment of mucosal and invasive candidiasis. Fluconazole prophylaxis in patients admitted to an ICU can reduce the incidence of invasive candidal infections. However, the use of prophylactic fluconazole in critical care patients can promote the emergence of non-albicans species, some of which are less susceptible or resistant to fluconazole.\textsuperscript{11,15,16}

We describe an interventional study performed during 1999–2007 at the ICU of San Martino University Hospital of Genoa, Italy, with the aim of evaluating the effect of a fluconazole restriction policy on the incidence of albicans and non-albicans candidaemia.

Methods

Setting and definition of a candidaemia case

The ICU of the San Martino University Hospital in Genoa, Italy, is a mid-size medical and surgical unit with 18 beds and ~500 admissions per year. The number of annual admissions ranged from 478 in 1999 to 501 in 2007, with no significant variation during the period of the study. In this setting, antifungal prophylaxis with fluconazole was extensively administered, even in patients without classical risk factors, in the period January 1999–December 2002. From January 2003, infectious disease consultants strongly discouraged this strategy and its use. Measures recommended for the prevention of nosocomial infections were introduced in the ICU before the study period: reservoir identification; prevention of cross-transmission; carrier identification; use of a gel hand rub containing alcohol for hand hygiene during patient care; isolation of ICU inpatients in single bedrooms; and reduction of intravenous catheter indwelling.

Patients who developed a clinically and microbiologically documented candidaemia were identified through a microbiological laboratory survey, and data were recorded in an electronic database. A review of patient charts was performed in order to identify clinically relevant episodes. Candidaemia was defined as at least one positive blood culture yielding Candida spp. in patients with fever or other clinical signs of infection. Nosocomial candidaemia was defined as a candidaemia occurring \( \geq 48 \) h after admission. Demographic and clinical characteristics of the patient population were determined. All the patients consented to participation in the study and publication of the results.

Microbiological procedures and fluconazole use

During the study period there were no changes in microbiological laboratory techniques. Candida spp. were isolated from blood using the BACTEC 860 system (Becton Dickinson, Inc., Sparks, MD, USA). The species were identified using the API-32C system (bioMerieux Vitek, Inc., St Louis, MO, USA).

Data concerning the consumption of fluconazole were extracted from the hospital pharmacy computer system. Antifungal agents were categorized using the Anatomical Therapeutic Chemical classification index with 2005 WHO defined daily doses (DDDs) (http://www.whocc.no/atcddd/indexdatabase). We calculated the DDD of fluconazole per 1000 patient-days.

Outcomes and statistical analysis

The main outcome of the study is the evaluation of the restriction policy in terms of change in fluconazole use, and in incidence of C. albicans and non-albicans bloodstream infections. Periods of 6 months were considered for statistical analysis.

The analysis of intervention was carried out with a segmented regression analysis of the interrupted time series according to the guidelines of the ORION statement, using the SegReg software.\textsuperscript{17} The selection of the best breakpoint and the best-fitting function type was based on maximizing the statistical coefficient of explanation and performing tests of significance. The relation between the dependent variable \( Y \) and the independent variable is described by the best-fitting function selected from seven types: type 0, a single horizontal line without breakpoint (no relation); type 1, a single sloping line without breakpoint; type 2, two connected segments with sloping lines; type 3, a horizontal segment followed by a sloping line; type 4, a sloping segment followed by a horizontal line; type 5, two horizontal segments at different levels; and type 6, two disconnected segments with sloping lines. Type 0 is used when type 1 has an insignificant regression coefficient (RC), type 1 is used when its correlation coefficient (CC) is higher than the explanation coefficient (EC) of types 2–6, type 2 is used when the two RCs (RC1 and RC2) are significant and are significantly different at 95%, and type 3 is used when the RC value to the left of the breakpoint (RC1) is insignificant and the RC value to the right (RC2) is significant at 95%. Type 4 is used when RC1 is 95% significant and RC2 is not, type 5 is used when RC1 and RC2 are both insignificant while the average \( Y \) values to the left and right of the breakpoint differ significantly at \( \geq 95\% \), and type 6 is used when both RCs are significant at 95% and the lines have significantly different \( Y \) values at the breakpoint.

Ethics

In our institution it is not necessary to gain ethics committee approval for this type of research.

Results

During the 108 month observational period (January 1999–December 2007), a total of 213 episodes of candidaemia were recorded in our ICU, with a 6 monthly average incidence of 1.42 episodes/10000 patient-days/year (range 0.36–3.02 episodes). Patient characteristics for C. albicans and non-albicans infections are shown in Table 1. No significant differences in sex, age, central venous catheterization or parenteral nutrition were found between the two groups. Non-albicans candidaemia was significantly more frequent in patients with a higher Apache II score and solid tumour (\( P < 0.05 \)). Overall, 46% of the
episodes (98/213) were due to *C. albicans*, followed by *Candida parapsilosis* (46/213, 22%) and *C. glabrata* (28/213, 13%).

The 6 month period incidence of candidaemia and fluconazole consumption, and the segmented regression analysis of interrupted time series results are reported in Figure 1 and Table 2. Segmented regression analysis of the interrupted time series showed that intervention resulted in a significant reduction in fluconazole use from the second semester of 2002: between the first semester of 1999 and the optimal breakpoint (second semester of 2002) the fluconazole use increased from 17 to 59 DDD/10000 patient-days, while after the second semester of 2002 it constantly decreased, reaching a value of 18–20 DDD/10000 patient-days. The effect of change in fluconazole prophylactic strategy led to a reduction in the consumption

### Table 1. Patient characteristics for *C. albicans* and non-*albicans* infections

<table>
<thead>
<tr>
<th>Characteristics</th>
<th><em>C. albicans</em> (n=98)</th>
<th>Non-<em>albicans</em> (n=115)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>54 (55)</td>
<td>76 (66)</td>
<td>NS</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>44 (45)</td>
<td>39 (34)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years), mean±SD</td>
<td>57.9±16.65</td>
<td>60.2±13.75</td>
<td>NS</td>
</tr>
<tr>
<td>Central venous catheterization, n (%)</td>
<td>84 (86)</td>
<td>107 (93)</td>
<td>NS</td>
</tr>
<tr>
<td>Parenteral nutrition, n (%)</td>
<td>53 (54)</td>
<td>70 (61)</td>
<td>NS</td>
</tr>
<tr>
<td>Apache II score, mean±SD</td>
<td>21.75±7.38</td>
<td>23.44±8.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Principal reasons for admission in ICU, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>surgery</td>
<td>37 (38)</td>
<td>43 (37)</td>
<td>NS</td>
</tr>
<tr>
<td>haematological malignancies</td>
<td>8 (8)</td>
<td>10 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>solid-organ transplant</td>
<td>8 (8)</td>
<td>10 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>trauma</td>
<td>17 (17)</td>
<td>12 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>burn</td>
<td>6 (6)</td>
<td>3 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>solid tumour</td>
<td>15 (15)</td>
<td>35 (30)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>other</td>
<td>7 (7)</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>total</td>
<td>98 (100)</td>
<td>115 (100)</td>
<td></td>
</tr>
</tbody>
</table>

NS, not significant.
of 96 DDD/10000 patient-days in the second semester of 2007 (Table 2).

The incidence of fungaemia due to \textit{C. albicans} was substantially stable (RC $0 \pm 0.01$) between the first semester of 1999 and the second semester of 2003 (intercept $0.37/10000$ patient-days); segmented regression analysis showed that after the breakpoint the incidence remained stable (RC $0 \pm 0.01$) and was lower (intercept $0.14/10000$ patient-days). The incidence of non-\textit{albicans} fungaemia increased between the first semester of 1999 and the second semester of 2003 (RC $0.14 \pm 0.02$, intercept $-0.17/10000$ patient-days). In the second semester of 2003, a dramatic drop was observed from $0.33$ to $0.04/10000$ patient-days and this remained stable to the end of the study (RC $0 \pm 0.09$, intercept $0/10000$ patient-days). The effect of the change in fluconazole use is quantified as a decrease in the incidence of \textit{albicans} and non-\textit{albicans} candidaemia of $0.23$ and $2.31/10000$ patient-days in the second semester of 2007, respectively.

**Discussion**

In our setting, fluconazole use constantly increased between the first semester of 1999 and the second semester of 2002. In the same period, we observed a shift towards non-\textit{albicans} strains in invasive candidiasis episodes. Thanks to a change in the prophylactic strategy, the use of fluconazole in our ICU dropped during 2002–07 (Table 2). Subsequently, a substantial reduction in candidaemia due to non-\textit{albicans} strains was reported from the second semester of 2003.

In the literature, the use of antifungal prophylaxis in ICU patients is controversial. This kind of approach seems very attractive, since morbidity and mortality rates in critically ill patients with invasive candidiasis are high. Additionally, prophylactic regimens have already been validated in chemotherapy-induced neutropenia, stem cell transplant recipients with neutropenia and solid-organ (liver, pancreas and small bowel) transplant recipients.\textsuperscript{16} Cruciani \textit{et al.,}\textsuperscript{18} in a systematic review and meta-analysis, evaluated systemic antifungal prophylaxis in non-neutropenic, critically ill, ICU adult patients. Analysing nine randomized clinical trials, the authors reported a decrease in incidence of invasive candidaemia, mortality rate due to \textit{Candida} infection and overall mortality in ICU patients who underwent prophylactic regimens. However, subsequent analysis did not confirm the association between azole prophylaxis and improvement of survival rates in invasive candidiasis.\textsuperscript{19,20} Moreover, the effect of prophylaxis on fungal resistance patterns is unclear. Cruciani \textit{et al.}\textsuperscript{18} did not register a shift in \textit{Candida} spp. to strains less susceptible to azoles, but the trial did not investigate the development of resistance over time. In a meta-analysis performed by Shorr \textit{et al.}\textsuperscript{20} data from the reports reviewed were insufficient to evaluate the impact of fluconazole prophylaxis on the distribution of non-\textit{albicans} species and on the emergence of antifungal resistance.

The present study was an uncontrolled observational study in a single hospital. Confounding factors cannot be excluded, but the role of any possible unidentified confounding variables is thought to be minimal; infection control policies were consistently applied to all patients during the study period. Our study found a clear correlation between fluconazole use control and decreasing incidence of non-\textit{albicans} candidaemia. Another
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point of particular interest in our experience is the time to event. In fact, fluconazole use was reduced after the second semester of 2002, while the incidence of non-albicans candidaemia dropped in the second semester of 2003, 1 year after the intervention. Moreover, at the same time the incidence of C. albicans fungae-

mia did not increase. Thus, the reduced use of fluconazole was not associated with a significant change in the frequency of invasive candidiasis due to C. albicans. The global ecology from 2003 returned as expected, with a predominance of C. albicans aetiology.

The latest guidelines of the Infectious Diseases Society of America, recently published, recommend antifungal prophylaxis only for high-risk patients admitted to an ICU with very high rates of invasive candidiasis (>10%) compared with normal rates of 1%–2%.

These recommendations reflect the absence of a survival benefit and the potential for both resistance and emer-

gence of non-albicans isolates associated with this strategy.

In conclusion, even if fluconazole remains a first-line treatment option in several cases of invasive candidiasis, its prophylactic use should be carefully evaluated. Using knowledge of local epidemiologic trends in Candida spp. to guide therapeutic choices is essential.

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Transparency declarations

No competing interests to declare.

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