# A practice-based observational study on the use of micafungin in Surgical Critical Care Units

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## ABSTRACT

**Introduction.** Echinocandins are first-line therapy in critically ill patients with invasive *Candida* infection (ICI). This study describes our experience with micafungin at Surgical Critical Care Units (SCCUs).

**Methods.** A multicenter, observational, retrospective study was performed (12 SCCUs) by reviewing all adult patients receiving 100 mg/24h micafungin for ≥72h during admission (April 2011-July 2013). Patients were divided by ICI category (possible, probable + proven), 24h-SOFA (<7, ≥7) and outcome.

**Results.** 72 patients were included (29 possible, 13 probable, 30 proven ICI). Forty patients (55.6%) presented SOFA ≥7. Up to 78.0% patients were admitted after urgent surgery (64.3% with SOFA <7 vs. 90.3% with SOFA ≥7, p=0.016), and 84.7% presented septic shock. In 66.7% the site of infection was intraabdominal. Forty-nine isolates were recovered (51.0% *C. albicans*). Treatment was empirical (59.7%), microbiologically directed (19.4%), rescue therapy (15.3%), or anticipated therapy and prophylaxis (2.8% each). Empirical treatment was more frequent (p<0.001) in possible versus probable + proven ICI (86.2% vs. 41.9%). Treatment (median) was longer (p=0.002) in probable + proven versus possible ICI (13.0 vs. 8.0 days). Favorable response was 86.1%, without differences by group. Age, blood *Candida* isolation, rescue therapy, final MELD value and %MELD variation were significantly higher in patients with non-favorable response. In the multivariate analysis ($R^2$=0.246, p<0.001) non-favorable response was associated with positive %MELD variations (OR=15.445, 95%CI= 2.529-94.308, p=0.003) and blood *Candida* isolation (OR=11.409, 95%CI=1.843-70.634, p=0.009).

**Conclusion.** High favorable response was obtained, with blood *Candida* isolation associated with non-favorable response, in this series with high percentage of patients with intraabdominal ICI, septic shock and microbiological criteria for ICI.

**Key words:** Micafungin; invasive *Candida* infection; intraabdominal; septic shock; Surgical Critical Care Unit

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## Estudio observacional basado en la práctica clínica sobre la utilización de micafungina en Unidades de Cuidados Críticos Quirúrgicos

## RESUMEN

**Introducción.** Las equinocandinas son tratamiento de primera línea en pacientes críticos con infección invasiva por *Candida* (IIC). Este estudio describe nuestra experiencia con micafungina en Unidades de Cuidados Críticos Quirúrgicos (UCCQs).

**Métodos.** Se realizó un estudio multicéntrico, observacional y retrospectivo (12 UCCQs) revisando todos los pacientes adultos que recibieron 100 mg/24h micafungina durante ≥72h tras su admisión en la UCCQ (Abril 2011-Julio 2013). Los pacientes se dividieron según la categoría de IIC (posible, probable + probada), valor de SOFA (<7, ≥7) y evolución.

**Resultados.** Se incluyeron 72 pacientes (29 posible, 13 probable y 30 IIC probadas). Cuarenta pacientes (55,6%) presentaron SOFA ≥7. Un total de 78,0% pacientes fueron ingresados tras cirugía urgente (64,3% con SOFA <7 vs. 90,3% con SOFA ≥7, p=0,016) y un 84,7% presentó shock séptico. El 66,7% de pacientes presentaban infección intraabdominal. Se recuperaron 49 aislados (51,0% *C. albicans*). El tratamiento fue empírico (59,7%), dirigido microbiológicamente (19,4%), terapia de rescate (15,3%), o anticipado y profilaxis (2,8% cada uno). El tratamiento empírico fue más frecuente (p<0,001) en IIC posible versus probable + probada (86,2% vs. 41,9%). La duración del tratamiento (mediana) fue mayor (p=0,002) en IIC probable + probada que en IIC posible (13,0% vs. 8,0%). La respuesta clínica fue favorable en el 86,1% sin diferencias por grupo. La edad, el aislamiento de sangre, la terapia de rescate, el valor de MELD final y la variación de MELD fueron significativamente

superiores en pacientes con respuesta clínica no favorable. En el análisis multivariado ($R^2$=0,246, p<0,001) la respuesta no favorable se asoció con variación positiva del MELD (OR=15,445, 95%IC= 2,529-94,308, p=0,003) y aislamiento de *Candida* en sangre (OR=11,409, 95%IC=1,843-70,634, p=0,009).

**Conclusión:** Se obtuvo una alta tasa de respuesta favorable, con el aislamiento de *Candida* en sangre asociado con respuesta no favorable en esta serie de pacientes con alto porcentaje de IIC intraabdominal, shock séptico e IIC con criterios microbiológicos.

**Palabras clave:** Micafungina; infección invasiva por *Candida*; intraabdominal; shock séptico; Unidad de Cuidados Críticos Quirúrgicos

## INTRODUCTION

Over the past decades *Candida* has emerged as an invasive pathogen in the intensive care unit (ICU) setting, with case fatality rates higher than those for bacterial sepsis; nevertheless, most *Candida* sepsis cases do not receive effective treatment within 24h of hypotension[1]. Presence and duration of central venous catheters, corticotherapy, neutropenia, solid tumour and mechanical ventilation have been identified as risk factors for invasive *Candida* infection (ICI) by non-*albicans Candida* species[2], a subset of *Candida* species increasing in the ICU setting[3], and recent gastrointestinal surgery for ICI by *Candida albicans*[2].

The subset of patients with recent intraabdominal events are at a uniquely risk for ICI[4] by *C. albicans*. In this context common risk factors, progressive colonization and invasion do not matter when a perforation of the hollow viscus releases *Candida* cells contained in the bowel flora within the peritoneum[5]. Culture rates of yeast from intraabdominal samples during intraabdominal surgery are >30% and they are associated with complicated postoperative courses[6]. Involvement of *Candida* is determined in around 20-30% of secondary peritonitis[7], *Candida* peritonitis being a frequent and life-threatening complication in surgical critically ill patients[5]. ICU patients with hospital-acquired sepsis represent a group at high-risk for development of ICU-acquired candidemia[8]. *Candida* bloodstream infections occur at highest rate in the ICU, accounting for 33-55% of all candidemias[4], and where it has been reported that 17% of ICU-acquired infections are caused by *Candida* spp[9]. Patients with candidemia have a higher ICU crude mortality rate than patients without candidemia (52.6% versus 20.6%), as has been reported in a study in our country[10], and when complicated by septic shock, mortality can exceed 60%[11,12]. Mortality rates directly attributable to candidemia have been reported to be 20-31%[13].

Although *C. albicans* remains the most frequent isolate of *Candida* bloodstream infections, it is documented that one-third of these infections are caused by non-*albicans* species, *Candida glabrata* and *Candida krusei* being the most common in previous studies, an important fact since they are generally non-susceptible to fluconazole[8].

Echinocandins are today the most potent drugs against *Candida* spp. (except *C. parapsilosis*) and are thereby recommended as first-line therapy in critically ill patients[14]. Micafungin, the last echinocandin approved in Europe, exhibits high intrinsic activity against main species of the genus *Candida*[15].

The aim of this study was to describe our experience with micafungin in the treatment of ICI in critically ill patients admitted to Surgical Critical Care Units (SCCUs).

## PATIENTS AND METHODS

A multicentre observational study was carried out in 12 Spanish hospitals. A retrospective analysis was performed on prospectively acquired data recorded in medical records of all adult patients that had received 100 mg/24h of micafungin for ≥72h during admission to Surgical Critical Care Units (SCCUs) from April 2011 to July 2013. Demographic, clinical and microbiological data, details of micafungin treatment, length of SCCU stay and of hospitalization, outcome of ICI and all-cause mortality in the SCCU or during hospitalization were recorded. The informed consent was waived due to the observational and retrospective nature of the study. The study protocol was approved by the Ethics Committee of each participating hospital.

Sequential Organ Failure Assessment (SOFA)[16] and Simplified Acute Physiology Score (SAPS II)[17] scores were calculated with data at admission (or within the first 24h) to the SCCU, and patients were divided by SOFA values (<7 or ≥7). The MELD (Model for End-stage Liver Disease) score[18] was calculated at initiation and at the end of micafungin treatment, and the percentage of variation was determined (final versus initial value) for each patient.

Patients were classified as with proven ICI (isolation of *Candida* from blood or sample from a sterile site or histopathological confirmation), probable ICI (host factors plus clinical criteria plus mycological evidence) or possible ICI (host factors plus clinical criteria without mycological support) following the EORTC criteria[19]. Use of micafungin treatment was classified as prophylaxis, anticipated therapy (colonization plus positive biomarker), empirical (severe sepsis without microbiological identification), microbiologically directed, or rescue therapy (due to failure or toxicity of previous antifungals).

Favourable outcome was defined as resolution of signs/symptoms of ICI with microbiological eradication or presumed eradication, and non-favourable outcome as absence of clinical response or adverse events leading to changes in antifungal treatment.

Comparisons between proportions were performed by the Chi-square test and the Fisher's exact test, when necessary. For quantitative variables, since data did not show normality in the Kolmogorov – Smirnoff test, the Kruskal-Wallis and Mann-Whitney tests, when necessary, were used. For data analysis, patients categorized as with probable ICI were pooled with those categorized as with proven ICI. Comparisons of all variables were performed comparing 1) patients with probable or proven ICI versus patients with possible ICI, 2) patients with SOFA <7 versus those with

SOFA ≥7 and 3) patients with favourable outcome versus those with non-favourable outcome of ICI. Logistic regression models (step–wise procedure) were performed using as dependent variable "non-favourable outcome of ICI" and as independent variables those showing differences (p≤0.1) in bivariate analyses. Interactions and linear dependence between independent variables were previously controlled. The model showing the maximum parsimony (the lowest number of variables with no significant reduction in the value of the determination coefficient) and the highest $R^2$ was considered. Statistical analyses were performed using SPSS v 14 programme (SPSS Inc., Chicago IL).

## RESULTS

A total of 72 patients were included, 43 presenting mycological criteria (13 with probable plus 30 with proven ICI) and 29 without it (possible ICI). A total of 40 (55.6%) patients presented SOFA values ≥7 at admission. The percentage of patients with possible, probable or proven ICI did not differ by values of SOFA at admission: 40.6%, 25.0% and 34.4%, respectively, among patients with SOFA <7, and 40.0%, 12.5% and 47.5%, respectively, among those with SOFA ≥7. Table 1 shows demographic data and host/ predisposing factors for ICI in global and distributing patients by ICI category or by SOFA group (SOFA<7 or ≥7). Among patients with SOFA ≥7, the percentage of patients presenting hemodynamic instability or undergoing dialysis was significantly higher than among patients with SOFA <7.

Twenty-one patients had been previously treated with antifungals, 19 of them (90.5%) with fluconazole. Among these previously-treated patients, the percentage of probable or proven ICI was higher, although not statistically significant (table 1).

Table 2 shows severity of patients at admission to SCCUs and sites of infection. Most patients came from the operating room (most of them after urgent surgery), with only 2.8% patients coming from the Emergency department. The most frequent site of infection was intraabdominal (66.7% of total patients), regardless the ICI category or the SOFA group. Values of SAPS II and SOFA scores were similar in the group of patients with possible and in those with probable + proven ICI. At admission, the most frequent affected organ/system (SOFA>2) were the cardiovascular, respiratory and renal systems, and up to 84.7% patients presented septic shock, without differences by ICI category.

In the 43 patients with mycological criteria (probable + proven ICI), presence of *Candida* was evidenced by biopsy (one patient) or positive culture of appropriate sample (42 patients). Only one species was found in 83.3% patients and 2 species in 16.7% patients. Among the 49 *Candida* isolates, the most frequent species was *Candida albicans* (25/49, 51.0%) followed by *Candida glabrata* (13/49, 26.5%), *Candida tropicalis* (5/49,

**Table 1** **Demographic data and host/predisposing factors for ICI in global and distributed by ICI category and by SOFA <7 or ≥7 at admission; n (%) except where indicated**

| Variables | Total (n=72) | By ICI category | | | By SOFA value | | |
|---|---|---|---|---|---|---|---|
| | | Possible (n=29) | Probable + Proven (n=43) | p | SOFA <7 (n=32) | SOFA ≥7 (n=40) | p |
| Age (mean ± SD) | 66.0 ± 11.7 | 63.6 ± 11.5 | 67.7 ± 11.6 | 0.144 | 63.3 ± 11.6 | 68.2 ± 11.4 | 0.079 |
| Males | 43 (59.7) | 18 (62.1) | 25 (58.1) | 0.739 | 18 (56.3) | 25 (62.5) | 0.591 |
| Malignancies | 25 (34.7) | 13 (44.8) | 12 (27.9) | 0.110 | 13 (40.6) | 12 (30.0) | 0.386 |
| Neutropenia (<500/mm$^3$) | 2 (2.8) | 0 (0.0) | 2 (4.7) | 0.512 | 0 (0.0) | 2 (5.0) | 0.499 |
| Diabetes mellitus | 15 (20.8) | 3 (10.3) | 12 (27.9) | 0.084 | 6 (18.8) | 9 (22.5) | 0.697 |
| Hemodynamic instability | 59 (81.9) | 23 (79.3) | 36 (83.7) | 0.633 | 21 (65.6) | 38 (95.0) | 0.002 |
| Dialysis | 25 (34.7) | 9 (31.0) | 16 (37.2) | 0.540 | 5 (15.6) | 20 (51.3) | 0.002 |
| Undergone major surgery | 71 (98.6) | 29 (100) | 42 (97.7) | 1.000 | 32 (100) | 39 (97.5) | 1.000 |
| Central catheter | 72 (100) | 29 (100) | 43 (100) | 1.000 | 32 (100) | 40 (100) | 1.000 |
| Parenteral nutrition | 61 (84.7) | 22 (75.9) | 39 (90.7) | 0.105 | 27 (84.4) | 34 (85.0) | 0.942 |
| Previous treatment with | | | | | | | |
| Steroids | 33 (45.8) | 11 (37.9) | 22 (51.2) | 0.269 | 12 (37.5) | 21 (52.5) | 0.247 |
| Immunosuppressants | 6 (8.3) | 2 (6.9) | 4 (9.3) | 1.000 | 3 (9.4) | 3 (7.9) | 1.000 |
| Broad-spectrum antibiotics >7 days | 58 (80.6) | 23 (79.3) | 35 (81.4) | 0.826 | 25 (78.1) | 33 (82.5) | 0.641 |
| Antifungals | 21 (29.2) | 5 (17.2) | 16 (37.2) | 0.081 | 9 (28.1) | 12 (30.0) | 0.929 |
| Median ($P_{25}$-$P_{75}$) duration (days) | 14.0 (9.5-16.5) | 11.0 (9.5-24.0) | 14.0 (7.8-15.8) | 0.901 | 15.0 (10.0-22.0) | 12.5 (4.0-16.5) | 0.310 |

**Table 2** **Severity and site of infection in global and distributing patients by ICI category or by SOFA <7 or ≥7 at admission. Data expressed as n (%) except where indicated**

| Variables | Total (n=72) | By ICI category | | | By SOFA value | | |
|---|---|---|---|---|---|---|---|
| | | Possible (n=29) | Probable + Proven (n=43) | p | SOFA <7 (n=32) | SOFA ≥7 (n=40) | p |
| Admission from the operating room | 59 (81.9) | 25 (86.2) | 34 (79.1) | 0.645 | 28 (87.5) | 31 (77.5) | 0.273 |
| After urgent surgery | 46 (78.0) | 19 (76.0) | 27 (79.4) | 0.754 | 18 (64.3) | 28 (90.3) | 0.016 |
| SAPS II at admission (mean ± SD) | 44.0 ± 7.7 | 44.2 ± 14.8 | 43.2 ± 14.8 | 0.931 | 34.1 ± 15.0 | 51.8 ± 14.3 | <0.001 |
| Affected organ/system (SOFA >2) at admission | | | | | | | |
| Respiratory | 47 (65.3) | 19 (65.5) | 28 (65.1) | 0.972 | 16 (50.0) | 31 (77.5) | 0.015 |
| Cardiovascular | 55 (76.4) | 25 (86.2) | 30 (69.8) | 0.107 | 17 (53.1) | 38 (95.0) | <0.001 |
| Renal | 33 (45.8) | 14 (48.3) | 19 (44.2) | 0.733 | 7 (21.9) | 26 (65.0) | <0.001 |
| Liver | 12 (16.7) | 3 (10.3) | 9 (20.9) | 0.338 | 5 (15.6) | 7 (17.5) | 0.832 |
| Coagulation | 22 (30.6) | 8 (27.6) | 14 (32.6) | 0.653 | 9 (28.1) | 13 (32.5) | 0.689 |
| Central Nervous System | 10 (13.9) | 3 (10.3) | 7 (16.3) | 0.475 | 0 (0.0) | 10 (25.0) | 0.002 |
| SOFA 24h after admission (mean ± SD) | 17.0 ± 3.7 | 7.6 ± 3.2 | 7.7 ± 4.0 | 0.911 | 4.3 ± 1.5 | 10.4 ± 2.6 | <0.001 |
| Median ($P_{25}$-$P_{75}$) time from admission to infection (days) | 9.0 (4.0-20.8) | 9.0 (2.0-15.0) | 11.0 (5.0-24.0) | 0.085 | 10.0 (3.5-19.8) | 9.0 (4.0-21.5) | 0.991 |
| Site of infection | | | | | | | |
| Peritonitis | 40 (55.6) | 18 (62.1) | 22 (51.2) | 0.361 | 14 (43.8) | 26 (65.0) | 0.071 |
| Intraabdominal abscess | 8 (11.1) | 3 (10.3) | 5 (11.6) | 1.000 | 4 (12.5) | 4 (10.0) | 1.000 |
| Others | 24 (33.3) | 8 (27.6) | 16 (37.2) | 0.396 | 14 (43.8) | 10 (25.0) | 0.093 |
| Septic shock | 61 (84.7) | 24 (82.8) | 37 (86.0) | 0.747 | 22 (68.8) | 39 (97.5) | 0.002 |

10.2%), *Candida parapsilosis* (3/49, 6.1%) and *Candida krusei* (3/49, 6.1%).

Micafungin treatment was empirical in 43 (59.7%) patients, microbiologically directed in 14 (19.4%), recue therapy in 11 (15.3%), anticipated therapy in 2 (2.8%), and prophylaxis in 2 (2.8%) patients. Micafungin was used as rescue therapy in 10 patients due to failure and in one patient because of toxicity of previous antifungals. No differences in type of treatment were found when comparing patients with SOFA <7 and those with SOFA ≥7. However, empirical treatment was significantly more frequent in the group of possible versus in probable + proven ICI (86.2% vs. 41.9%, p<0.001) and microbiologically directed treatment in probable + proven ICI (3.4% vs.30.2%, p=0.012). Table 3 shows length of micafungin treatment, length of stay and outcome. Median duration of micafungin treatment was 11 days, with significantly longer duration in patients with probable or proven ICI than in those with possible ICI. Association of antifungals was used in 10 patients (7 with probable or proven ICI and 3 with possible ICI), without differences by SOFA group. The most frequent combination was with fluconazole (4/10, 40.0%). Micafungin was well tolerated, with only one related adverse event consisting of hyperbilirubinemia in a patient with possible ICI and SOFA ≥7.

Median length of SCCU and hospital stay were 23.5 and 47.5 days, respectively, without differences by ICI category or SOFA group. The overall favourable response was 86.1%, without differences between study groups.

Table 4 shows significant variables in the bivariate analysis distributing patients by favourable (n=62) versus non-favourable (n=10) outcome. In addition, previous administration of broad-spectrum antibiotic, which was more frequent among patients with favourable (83.9%) than among those with non-favourable (60.0%) outcome, although non-significant, was also introduced as independent variable in the multivariate analysis since the value of p was <0.1 (p=0.095).

The multivariate analysis ($R^2$=0.246, p<0.001) showed that non-favourable response of ICI was associated with positive variations in MELD values (greater final than initial values) (OR=15.445, 95%CI= 2.529-94.308, p=0.003) and isolation of *Candida* from blood sample (OR=11.409, 95%CI=1.843-70.634, p=0.009).

## DISCUSSION

An increase in the number of high-risk patients and surgical technique complexity has driven to the increase in *Candida*-related infections at SCCUs. Echinocandins are recommended as first-line therapy in critically ill patients[14]. In the present study we described the management of ICI with micafungin, the last echinocandin approved in Europe, in patients admitted to our

**Table 3** **Length of treatment, length of stay and outcome, in global and distributing patients by ICI category or by SOFA <7 or ≥7 at admission. Data expressed as median ($P_{25}$-$P_{75}$) except where indicated**

| Variables | Total (n=72) | By category | | | By SOFA value | | |
|---|---|---|---|---|---|---|---|
| | | Possible (n=29) | Probable + Proven (n=43) | p | SOFA <7 (n=32) | SOFA ≥7 (n=40) | p |
| Length of micafungin treatment (days) | 11.0 (7.0-17.0) | 8.0 (6.0-10.5) | 13.0 (8.0-18.0) | 0.002 | 10.0 (7.0-14.0) | 11.0 (6.0-20.0) | 0.789 |
| MELD score value | | | | | | | |
| At initiation of micafungin treatment | 13.0 (9.0-21.0) | 13.0 (9.0-18.5) | 13.0 (9.0-22.0) | 0.388 | 10.0 (8.3-16.5) | 17.0 (10.3-22.8) | 0.031 |
| At end of micafungin treatment | 11.0 (8.0-19.5) | 11.0 (8.5-19.0) | 11.0 (8.0-20.0) | 0.922 | 9.0 (8.0-14.3) | 14.5 (9.0-20.0) | 0.056 |
| Length of stay in the SCCU (days) | 23.5 (13.3-45.8) | 23.0 (11.5-36.5) | 25.0 (14.0-45.0) | 0.265 | 25.5 (15.3-50.3) | 22.5 (12.3-44.0) | 0.451 |
| Length of hospitalization | 47.5 (36.5-83.5) | 42.0 (36.0-79.5) | 54.0 (36.0-86.0) | 0.484 | 57.5 (39.5-94.7) | 45.0 (33.0-82.8) | 0.451 |
| Outcome of ICI, n (%) | | | | | | | |
| Favourable | 62 (86.1) | 26 (89.7) | 36 (83.7) | 0.730 | 29 (90.6) | 33 (82.5) | 0.322 |
| Recurrence | 6 (8.3) | 3 (10.3) | 3 (7.0) | 0.679 | 3 (9.4) | 3 (7.5) | 1.000 |
| All-cause mortality in the SCCU, n (%) | 22 (30.6) | 9 (31.0) | 13 (30.0) | 0.942 | 7 (21.9) | 15 (37.5) | 0.153 |
| In-hospital all-cause mortality, n (%) | 27 (37.5) | 12 (41.4) | 15 (34.9) | 0.577 | 9 (28.1) | 18 (45.0) | 0.142 |

SCCUs. From this analysis we found that among patients receiving micafungin in our SCCUs, a high percentage were patients with intraabdominal infection (66.7%), with septic shock (84.7%), and with microbiological criteria for ICI (59.7% with probable or proven ICI), with a total of 41.7% patients with proven ICI. This study population profile is in accordance with the participating hospital wards, SCCUs, where, as in our study, most patients come from the operating room after urgent surgery. Among others, the presence of severe sepsis/septic shock should alert of the possibility of *Candida* involvement in intraabdominal infections[20], since the subset of patients with recent intraabdominal events are at a uniquely risk for ICI[4]. In general ICUs, the reported percentage of severe sepsis/septic shock associated with ICI is 8-30%/23-38%[11,21,22]. In our series, in SCCUs with high number of patients with intraabdominal infections, the percentage of patients presenting septic shock was markedly higher than those reported in general ICUs.

Not all species of the genus *Candida* exhibit the same pathogenic potential and antifungal susceptibility profile. *Candida* species, frequent colonizers occasionally producing infection, are not especially invasive organisms. Nevertheless, while *C. glabrata* is always a yeast and *C. parapsilosis* may present also pseudohyphae, *C. tropicalis* and *C. albicans* may produce true hyphae with intrinsic virulence factors regulating the transition from yeast to the filamentous phenotype[23,24]. In this sense, lower mortality rates for *C. parapsilosis* and higher for *C. tropicalis* when compared to other species have been reported[11]. During the last decade, there has been a shift towards increasing prevalence of non-*albicans Candida* in critically ill patients[25], *C. parapsilosis* (around 25% isolates) being the most frequent non-*albicans* species in ICUs in Spain[26]. However, in USA *C. glabrata* is the second cause of candidemia[27]. In the present series in Spanish SCCUs, the most frequent non-*albicans* species were *C. glabrata* (26.5%) and *C. tropicalis* (10.2%). This is important due to the relatively low percentage of susceptibility to fluconazole in non-*albicans Candida*[25]. The recent increase in fluconazole resistance has encouraged the use of other antifungals, as echinocandins[28], which are fungicidal. This, among other facts that point to the fact that there may be advantages of echinocandins over azoles[29], drive to current guidelines are now recommending initial treatment with echinocandins for all critically ill patients basically in all situations[4].

Coverage of *Candida* spp. in patients with high degree of intraabdominal contamination has been recommended[20,30]. Recent gastrointestinal surgery has been identified as risk factor for ICI by *C. albicans*[2], in our study representing 51% of all isolates in relation to the high number of patients with intraabdominal ICI. Since *Candida* infections with candidemia imply high mortality, exceeding 60% when complicated with septic shock[11,12,21], and the empirical approach depending on clinical suspicion is shown to result in better outcome[31], early empirical therapy is preferred and up to 70% of the antifungal therapy in the ICU is preventive/empirical[32,33]. Micafungin was used as empirical treatment in around 60% patients in the present study, being more frequent in possible than in probable + proven ICI cases where, as expected, microbiologically directed treatment was more frequent.

A previous multivariate analysis concluded that *C. albicans* (when compared with non-*albicans*) and inadequate antifungal therapy were associated with higher mortality rates[4]. In addition, each hour of delay in effective antifungal therapy during the first 6h of shock has been reported to cause a 7.6% reduction in survival[34]. In our study non favourable response was associated with isolation of *Candida* from blood, and all-cause in-hospital mortality was 37.5%, lower than previously

**Table 4** **Variables showing differences in bivariate analysis of patients with favourable outcome versus those with non-favourable outcome.**

| Variables | Total (n=72) | Favourable (n=62) | Non-favourable (n=10) | p |
|---|---|---|---|---|
| Age (mean ± SD) | 66.0 ± 11.7 | 65.1 ± 11.9 | 71.9 ± 8.6 | 0.046 |
| Previous fluconazole treatment[a] | 19/21 (90.5) | 16/16 (100) | 3/5 (60.0) | 0.001 |
| Isolation of *Candida* in blood culture, n (%) | 40 (55.6) | 31 (50.0) | 9 (90.0) | 0.035 |
| Micafungin as rescue therapy due to failure of other antifungals, n (%) | 10 (13.9) | 6 (9.7) | 4 (40.0) | 0.027 |
| Final MELD value, median ($P_{25}$,$P_{75}$) | 11.0 (8.0, 19.5) | 10.5 (8.0, 16.5) | 20.0 (13.0, 26.0) | 0.004 |
| % variation final MELD value with respect to initial value, median ($P_{25}$,$P_{75}$) | 0.0 (-0.27, 0.13) | -0.08 (-0.29, 0.03) | 0.38 (0.02, 0.49) | <0.001 |

[a]n/patients with previous antifungal treatment (%)

reported[10-12], and without significant differences between patients with SOFA <7 and ≥7.

One major limitation of the present study is its retrospective and non-comparative design which confer to results only a descriptive value. On the other hand, the fact that all patients with ICI treated with micafungin were included in 12 SCCUs during 2 years and that most of them presented ICI with mycological criteria, septic shock and intraabdominal infection offers a valuable perspective of micafungin treatment (mostly as empirical or microbiologically directed) in this specific subset of SCCU patients.

In conclusion, the results showed high favourable response with micafungin, with isolation of *Candida* from blood associated with non-favourable response in this series including a high percentage of patients with intraabdominal ICI, with septic shock and microbiological criteria for ICI.

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