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# Intraabdominal candidiasis in surgical ICU patients treated with anidulafungin: A multicenter retrospective study

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## ABSTRACT

**Introduction.** Patients with recent intraabdominal events are at uniquely risk for intraabdominal candidiasis (IAC). *Candida* peritonitis is a frequent and life-threatening complication in surgically ill patients. International guidelines do not specifically address IAC. This study describes clinical features of IAC in critical patients treated with anidulafungin in Surgical ICUs (SICUs).

**Material and methods.** A practice-based retrospective study was performed including all adults with IAC admitted to 19 SICUs for ≥24h treated with anidulafungin. IAC was documented (*Candida* isolation from blood/peritoneal fluid/abscess fluid and/or histopathological confirmation) or presumptive (host factors plus clinical criteria without mycological support). Total population and the subgroup of septic shock patients were analyzed.

**Results.** One hundred and thirty nine patients were included, 94 (67.6%) with septic shock, 112 (86.2%) after urgent surgery. Of them, 77.7% presented peritonitis and 21.6% only intraabdominal abscesses. Among 56.8% cases with documented IAC, *C. albicans* (52.8%) followed by *C. glabrata* (27.8%) were the most frequent species. Anidulafungin was primarily used as empirical therapy (59.7%), microbiologically directed (20.9%) and anticipated therapy (15.8%). Favourable response was 79.1% (76.6% among patients with septic shock). Intra-SICU mortality was 25.9% (28.7% among patients with septic shock).

**Conclusions.** Among IACs managed at SICUs, peritonitis was the main presentation, with high percentage of patients presenting septic shock. *C. albicans* followed by *C. glabrata* were the main responsible species. Anidulafungin treatment was mostly empirical followed by microbiologically directed therapy, with a favourable safety profile, even among patients with septic shock.

**Key words: Intraabdominal candidiasis; *Candida* peritonitis; Septic shock; Surgical ICU; Anidulafungin; Echinocandins**

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## Candidiasis intraabdominal en pacientes críticos quirúrgicos tratados con anidulafungina: estudio retrospectivo multicéntrico

## RESUMEN

**Introducción.** Los pacientes con cirugía intraabdominal reciente presentan alto riesgo de candidiasis intraabdominal (CIA). La peritonitis por *Candida* es una complicación frecuente y comporta riesgo vital en los pacientes críticos quirúrgicos. Las recomendaciones internacionales no abordan específicamente la CIA. Este estudio describe las características de la CIA en pacientes críticos tratados con anidulafungina ingresados en Unidades de Cuidados Críticos Quirúrgicos (UCCQs).

**Material y métodos.** Se llevó a cabo un estudio retrospectivo incluyendo a todos los pacientes con CIA ingresados en 19 UCCQs durante al menos 24h y tratados con anidulafungina. La CIA se consideró documentada cuando se aisló *Candida* de sangre/líquido peritoneal/absceso y/o hubo confirmación histopatológica, y presumible cuando estaban presentes factores del huésped y criterios clínicos sin aislamiento microbiológico. Se analizó el grupo total de pacientes, así como el subgrupo de pacientes que presentaban shock séptico por separado.

**Resultados.** Se incluyeron 139 pacientes, 94 (67,6%)

con shock séptico, 112 (86,2%) tras cirugía urgente. De ellos, 77,7% presentaban peritonitis y 21,6% absceso intraabdominal exclusivamente. Entre los 56,8% casos con CIA documentada, *C. albicans* (52,8%) seguido de *C. glabrata* (27,8%) fueron las especies más frecuentes. Anidulafungina se utilizó principalmente como tratamiento empírico (59,7%), dirigido (20,9%) o anticipado (15,8%). La respuesta fue favorable en el 79,1% de los pacientes (76,6% en pacientes con shock séptico). La mortalidad intra-UCCQ fue del 25,9% (28,7% en pacientes con shock séptico).

**Conclusiones.** Entre las CIAs tratadas en UCCQs, la peritonitis es la presentación clínica más frecuente, con un alto porcentaje de pacientes con shock séptico. *C. albicans* seguido de *C. glabrata* fueron las principales especies responsables de la infección. Anidulafungina se utilizó en la mayoría de casos como tratamiento empírico seguido de como tratamiento dirigido, con un perfil de seguridad favorable, incluso entre los pacientes que presentaban shock séptico.

**Palabras claves: Candidiasis intraabdominal; *Candida* peritonitis; Shock séptico; Unidades de Cuidados Críticos Quirúrgicos; Anidulafungina; Equinocandinas**

## INTRODUCTION

2012 ESCMID guidelines for the diagnosis and management of *Candida* disease in non-neutropenic adult patients strongly recommend (A-I evidence, "strong support") echinocandins as initial therapy of candidaemia[1]. This new class of antifungals is recommended for moderate to severely ill patients or patients with previous azole exposure by the IDSA guidelines[2]. Nowadays, the progressive approach appears to be treating all critically ill patients with invasive *Candida* infection (ICI) with echinocandins[3]. Echinocandins are concentration-dependent compounds, active against biofilm-producing strains and fungicidal against *Candida* spp. except for *Candida parapsilosis* (ICI by this species presents lower mortality rates than ICI by other species[4]). In contrast, fluconazole is fungistatic, time-dependent and has no activity against biofilm-producing strains[5]. The literature on anidulafungin supports its efficacy[6,7], and pharmacokinetic data from patients with septic shock and hemodialysis[8,9] support its use in critically ill patients[5].

Patients are frequently admitted to mixed (medical-surgical) Intensive Care Units (ICUs) because of multi-organ failure due to intraabdominal infection[10]. Since the subset of patients with recent intraabdominal events are at uniquely risk for intraabdominal candidiasis (IAC)[3], *Candida* peritonitis is a frequent and life-threatening complication in surgical patients[11,12], being associated with a poor prognosis[13]. IAC acquires special importance in surgical ICUs where high number of patients are admitted after high-risk intraabdominal surgical interventions.

The aim of the present study was to describe clinical features of IAC in a series of critically ill patients treated with anidulafungin in 19 Surgical ICUs (SICUs) in Spain.

## PATIENTS AND METHODS

A multicenter practice-based study was carried out in 19 Spanish SICUs. A retrospective analysis was performed on prospectively acquired data recorded in medical records of all adult patients with IAC admitted to SICUs for ≥24h and treated with anidulafungin (200 mg loading dose followed by 100 mg/day) from October 2010 to June 2012. 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.

Demographic, clinical, analytical and microbiological data, details of antifungal treatment, length of SICU stay and of hospitalization, outcome and mortality in the SICU were recorded. The *Candida* score[14], the Sequential Organ Failure Assessment (SOFA)[15] and the Simplified Acute Physiology Score (SAPS II)[16] scores were calculated with data at the time of initiation of anidulafungin treatment. IAC was categorized as documented (isolation of *Candida* from blood and/or peritoneal fluid and/or abscess fluid and/or histopathological confirmation) or presumptive (host factors plus clinical criteria without mycological support). Anidulafungin treatment was classified as prophylaxis, anticipated therapy in colonized patients, empirical (severe sepsis without microbiological identification), microbiologically directed, or rescue therapy (due to failure or toxicity of previous antifungals).

Favorable outcome was defined as complete clinical and microbiological resolution or improvement of signs/symptoms of IAC, and non-favorable outcome as persistence of infection, reinfection or change of anidulafungin by other antifungal.

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. Comparisons of all variables were performed distributing patients by outcome (favorable versus non-favorable) considering both total study population and only the subgroup of patients presenting septic shock. Logistic regression models (step–wise procedure) were performed using as dependent variable "non-favorable outcome" and as independent variables those showing differences ($p \leq 0.05$) 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 139 patients were included, 94 (67.6%) of them with septic shock at anidulafungin treatment initiation. A total of 112 (86.2%) patients had been admitted to the SICU after

**Table 1** **Clinical data. Demographic data, underlying conditions (in >10% patients) and clinical scores at treatment initiation in SICU; n (%) except indicated**

| | Total population | | | | Patients with septic shock | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Favorable | Non-favorable | p | Total | Favorable | Non-favorable | p |
| n | 139 | 110 | 29 | | 94 | 72 | 22 | |
| Age, mean ± SD | 64.5 ± 13.9 | 64.0 ± 14.1 | 66.6 ± 13.1 | 0.388 | 64.9 ± 13.5 | 66.2 ± 12.4 | 64.5 ± 13.8 | 0.605 |
| Males | 85 (61.2) | 69 (62.7) | 16 (55.2) | 0.458 | 57 (60.6) | 45 (62.5) | 12 (54.5) | 0.504 |
| COPD | 32 (23.0) | 21 (19.1) | 11 (37.9) | 0.032 | 23 (24.5) | 15 (20.8) | 8 (36.4) | 0.138 |
| Heart disease | 28 (20.1) | 21 (19.1) | 7 (24.1) | 0.547 | 17 (18.1) | 13 (18.1) | 4 (18.4) | 1.000 |
| Chronic renal disease | 15 (10.8) | 12 (10.9) | 3 (10.3) | 1.000 | 10 (10.6) | 8 (11.1) | 2 (9.1) | 1.000 |
| Chronic liver disease | 17 (12.2) | 11 (10.0) | 6 (20.7) | 0.198 | 13 (13.8) | 8 (11.1) | 5 (22.7) | 0.167 |
| Hemodynamic instability | 102 (73.2) | 79 (71.8) | 23 (79.3) | 0.416 | 90 (95.7) | 69 (85.8) | 21 (95.5) | 1.000 |
| Mechanical ventilation | 109 (78.4) | 85 (77.3) | 24 (82.8) | 0.523 | 86 (91.5) | 65 (90.3) | 21 (95.5) | 0.676 |
| Candida score, median ($P_{25}$,$P_{75}$) | 4.0 (3.0,4.0) | 3.0 (3.0,4.0) | 4.0 (3.0,4.0) | 0.077 | 4.0 (3.0,4.0) | 4.0 (3.0,4.0) | 4.0 (3.0,4.0) | 0.181 |
| SAPS, mean ± SD | 47.8 ± 15.5 | 46.7 ± 14.8 | 51.7 ± 17.7 | 0.128 | 52.4 ± 14.0 | 51.5 ± 13.2 | 55.2 ± 16.2 | 0.296 |
| Affected organ/system (SOFA >2) | | | | | | | | |
| Respiratory | 87 (62.6) | 67 (60.9) | 20 (69.0) | 0.425 | 65 (59.1) | 49 (68.1) | 16 (72.7) | 0.795 |
| Cardiovascular | 98 (70.5) | 73 (66.4) | 25 (86.2) | 0.041 | 86 (91.5) | 64 (88.9) | 22 (100) | 0.192 |
| Renal | 64 (46.0) | 45 (40.9) | 19 (65.2) | 0.018 | 50 (53.2) | 34 (47.2) | 16 (72.7) | 0.036 |
| CNS | 16 (11.5) | 9 (8.2) | 7 (24.1) | 0.017 | 13 (13.8) | 7 (9.7) | 6 (27.3) | 0.037 |
| Coagulation | 54 (38.8) | 40 (36.4) | 14 (48.3) | 0.242 | 42 (44.7) | 31 (43.1) | 11 (50.0) | 0.566 |
| Hepatic | 40 (28.8) | 29 (26.4) | 11 (37.9) | 0.221 | 26 (27.7) | 17 (23.6) | 9 (40.9) | 0.112 |

urgent surgery. One-hundred ten (79.1%) patients presented favorable response: 89 (80.9%) showing complete resolution and 21 (19.1%) improvement. Among 29 (20.9%) patients with non-favorable response, 19 (65.5%) presented persistence, 2 (6.9%) reinfection and in 8 (27.6%) patients anidulafungin was changed to other antifungal. In the subgroup of patients with septic shock, 72 (76.6%) patients presented favorable response (81.9% complete resolution and 18.1% improvement) and 22 (23.4%) non-favorable response (63.6% persistence, 9.1% reinfection and 27.3% change of anidulafungin).

Table 1 shows demographic data and underlying conditions in total population and in the subgroup of patients presenting septic shock. Mean age was 64.5 years and 61.2% patients were males. Among patients with non-favorable response percentages of patients presenting chronic obstructive pulmonary disease (COPD) and cardiovascular and/or central nervous system as affected system (SOFA>2) were higher than among those with favorable response, both considering total population and the subgroup of patients with septic shock. Median ($P_{25}$-$P_{75}$) values of CRP, lactate and procalcitonin were 35.85 (19.85-240.75) mg/l, 2.02 (1.20-3.40) mmol/l and 3.30 (1.11-14.38) ng/ml, respectively; the subgroup of patients with septic shock presenting higher values [39.2 (22.0-254.45) mg/l, 2.55 (1.57-3.62) mmol/l and 8.44 (1.99-33.52) ng/ml, respectively]. In both populations, no differences in values of biomarkers were found between patients with favorable and non-favorable response.

Table 2 shows risks factors for IAC, classification of cases as documented/presumptive IAC and type of intraabdominal infection. Most patients had undergone major surgery, presented vascular catheter and parenteral nutrition and had been previously treated with antibiotics. Distribution of cases as documented/presumptive IAC did not show differences between total population and patients with septic shock. Overall, 56.8% of all cases were documented IAC. Distribution by type of infection was similar in the total population and in patients with septic shock. In the total population, 77.7% patients presented peritonitis, 24.1% of them with concomitant intraabdominal abscess, while in 21.6% cases only intraabdominal abscesses were present.

Table 3 shows microbiological data in patients with documented IAC. *C. albicans* (52.8%) was the most frequent species isolated followed by *C. glabrata* (27.8%), without differences between patients with favorable and non-favorable response or between patients with and those without septic shock.

Table 4 shows antifungal treatment. Anidulafungin was used as empirical therapy in most patients (59.7%), followed

**Table 2** **Risk factors and type of ICI. Risks factors for ICI, classification of IAC cases, and type of intraabdominal infection; n (%)**

| | Total population | | | | Patients with septic shock | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Favorable | Non-favorable | p | Total | Favorable | Non-favorable | p |
| n | 139 | 110 | 29 | | 94 | 72 | 22 | |
| Neutropenia (<500/mm$^3$) | 8 (5.8) | 6 (5.5) | 2 (6.9) | 0.672 | 6 (6.4) | 4 (5.6) | 2 (9.1) | 0.622 |
| Major surgery | 128 (92.1) | 102 (92.7) | 26 (89.7) | 0.698 | 89 (94.7) | 70 (97.2) | 19 (86.4) | 0.082 |
| Vascular catheter | 135 (97.1) | 108 (98.2) | 27 (93.1) | 0.192 | 92 (97.9) | 72 (100) | 20 (90.9) | 0.053 |
| Malignancies | 49 (35.3) | 38 (34.5) | 11 (37.9) | 0.734 | 33 (35.1) | 26 (36.1) | 7 (31.8) | 0.712 |
| Parenteral nutrition | 111 (79.9) | 88 (80.0) | 23 (79.3) | 1.000 | 75 (79.8) | 59 (81.9) | 16 (72.7) | 0.346 |
| Chronic renal failure | 13 (9.4) | 10 (9.1) | 3 (10.3) | 0.734 | 9 (9.6) | 7 (9.7) | 2 (9.1) | 1.000 |
| Renal replacement therapy | 27 (19.4) | 20 (18.2) | 7 (24.1) | 0.471 | 22 (23.4) | 16 (22.2) | 6 (27.3) | 0.774 |
| Diabetes mellitus | 34 (24.5) | 27 (24.5) | 7 (24.1) | 0.964 | 24 (25.5) | 19 (26.4) | 5 (22.7) | 1.000 |
| Previous treatment with | | | | | | | | |
| Antibiotics | 110 (79.1) | 86 (78.2) | 24 (82.8) | 0.589 | 73 (77.7) | 54 (75.0) | 19 (86.4) | 0.383 |
| Steroids | 30 (21.6) | 21 (19.1) | 9 (31.3) | 0.164 | 20 (21.3) | 13 (18.1) | 7 (31.8) | 0.167 |
| Azoles | 50[a] (36.0) | 37 (33.6) | 13 (44.8) | 0.264 | 31 (33.0) | 23 (30.6) | 9 (40.9) | 0.366 |
| Presumptive IAC | 60 (43.2) | 50 (45.5) | 10 (34.5) | 0.289 | 43 (45.7) | 35 (48.6) | 8 (36.4) | 0.312 |
| Documented IAC | 79 (56.8) | 60 (54.5) | 19 (65.5) | 0.289 | 51 (54.3) | 37 (51.4) | 14 (63.6) | 0.312 |
| Peritonitis | 82 (59.0) | 66 (60.0) | 16 (55.2) | 0.638 | 59 (62.8) | 48 (66.7) | 11 (50.0) | 0.157 |
| Intraabdominal abscess | 30 (21.6) | 24 (21.8) | 6 (20.7) | 0.895 | 16 (17.0) | 11 (15.3) | 5 (22.7) | 0.514 |
| Both | 26 (18.7) | 19 (17.3) | 7 (24.1) | 0.399 | 19 (20.2) | 13 (18.1) | 6 (27.3) | 0.371 |
| Others[b] | 1 (0.7) | 1 (0.9) | 0 (0.0) | 1.000 | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |

[a]**Fluconazole in 48 patients (96.0%);** [b]**One hepatic abscess**

by microbiologically directed (20.9%) and anticipated therapy (15.8%). Only in a small number of cases (3.6%) anidulafungin was used as rescue therapy and in no cases as prophylaxis. Combined therapy was used in 24.5% patients in the total population and in 23.4% patients with septic shock, without significant differences between the groups of patients with favorable and non-favorable response. Fluconazole was the most frequent concomitant antifungal. No significant differences in favorable response were found between patients treated with anidulafungin alone and those treated with anidulafungin plus fluconazole, both in the total population [84/105 (80.0%) vs. 25/30 (83.3%), p=0.683] and in the subgroup of patients with septic shock [57/72 (79.2%) vs. 14/18 (77.8%), p=0.771].

Table 5 shows length of stay and mortality. Length of stay in the SICU was similar for patients with favorable and those with non-favorable response, both in the total population and among patients with septic shock. Intra-SICU mortality was 25.9% in the total population, rising to 28.7% among patients with septic shock.

In the multivariate analysis in the total population ($R^2$=0.102, p=0.001), non-favorable response was associated with central nervous system (OR=3.818, 95%CI=1.217, 11.980, p=0.022) or renal system (OR=2.761, 95%CI=1.132, 6.736, p=0.026) as affected organ/system (SOFA >2) and COPD (OR=2.971, 95%CI=1.162, 7.597, p=0.023) as underlying condition.

Only two adverse events were recorded, both in patients with documented IAC: a mild rash considered as drug-related and one severe renal insufficiency considered as no drug-related event.

## DISCUSSION

Thirty to forty percent of patients with secondary and tertiary peritonitis may develop IAC, mainly represented by *Candida* peritonitis or intraabdominal abscess[17]. Most published studies in critically ill patients include patients with different type of pathologies and candidemia treated at mixed (medical-surgical) ICUs and, unfortunately, international guidelines (focused on candidemia[2,18-20]) do not specifically address the particular setting of IAC[17] in surgical ICUs. IAC pathogenesis is different from medical candidemia since in IAC the yeast pathway is favored by anatomical breach. In this context, the

**Table 3** **Microbiological data. Microbiological data among patients with documented IAC; n (%)**

| | Total population | | | | Patients with septic shock | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Favorable | Non-favorable | p | Total | Favorable | Non-favorable | p |
| n | 79 | 60 | 19 | | 51 | 37 | 14 | |
| Samples | | | | | | | | |
| Blood | 16 (20.3) | 11 (18.3) | 5 (27.8) | 0.506 | 10 (19.6) | 8 (21.6) | 2 (14.3) | 1.000 |
| Peritoneal fluid | 52 (65.8) | 41 (68.3) | 11 (57.9) | 0.418 | 39 (76.5) | 30 (81.1) | 9 (64.3) | 0.272 |
| Abscess fluid | 28 (35.4) | 21 (35.0) | 7 (36.8) | 1.000 | 16 (31.4) | 11 (29.7) | 5 (35.7) | 0.742 |
| Species isolated | | | | | | | | |
| *C. albicans* | 46 (58.2) | 36 (60.0) | 10 (52.6) | 0.602 | 28 (54.9) | 22 (59.5) | 6 (42.9) | 0.353 |
| *C. glabrata* | 22 (27.8) | 19 (31.7) | 3 (15.8) | 0.245 | 14 (27.5) | 12 (32.4) | 2 (14.3) | 0.297 |
| *C. krusei* | 8 (10.1) | 7 (11.7) | 1 (5.3) | 0.672 | 5 (9.8) | 4 (10.8) | 1 (7.1) | 1.000 |
| *C. parapsilosis* | 5 (6.3) | 2 (3.3) | 3 (15.8) | 0.087 | 4 (7.8) | 1 (2.7) | 3 (21.4) | 0.058 |
| *C. tropicalis* | 3 (3.8) | 2 (3.3) | 1 (5.3) | 0.567 | 3 (5.9) | 2 (5.4) | 1 (7.1) | 1.000 |
| Other *Candida* | 2 (2.5) | 0 (0.0) | 2 (10.5) | 0.055 | 2 (3.9) | 0 (0.0) | 2 (14.3) | 0.087 |

**Table 4** **Treatment. Antifungal treatment: type and duration; n (%) except indicated**

| | Total population | | | | Patients with septic shock | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Favorable | Non-favorable | p | Total | Favorable | Non-favorable | p |
| **Anidulafungin** | | | | | | | | |
| n | 139 | 110 | 29 | | 94 | 72 | 22 | |
| Anticipated therapy | 22 (15.8) | 18 (16.4) | 4 (13.8) | 1.000 | 14 (14.9) | 11 (15.3) | 3 (13.6) | 1.000 |
| Empirical | 83 (59.7) | 67 (60.9) | 16 (55.2) | 0.575 | 60 (63.8) | 47 (65.3) | 13 (59.1) | 0.597 |
| Microbiologically directed | 29 (20.9) | 23 (20.9) | 6 (20.7) | 1.000 | 16 (17.0) | 12 (16.7) | 4 (18.2) | 1.000 |
| Rescue therapy | 5 (3.6) | 2 (1.8) | 3 (10.3) | 0.661 | 4 (4.3) | 2 (2.8) | 2 (9.1) | 0.232 |
| Length (days) of anidulafungin treatment, median ($P_{25}$,$P_{75}$) | 10.0 (6.0, 17.0) | 11.0 (6.0, 19.0) | 32.0 (15.5, 46.5) | 0.024 | 10.0 (6.0, 19.0) | 10.0 (6.3, 19.0) | 8.0 (3.0, 16.3) | 0.214 |
| **Patients with combined antifungal therapy** | | | | | | | | |
| n (%) | 34[a] (24.5) | 26 (23.6) | 8[a] (27.6) | 0.660 | 22[a] (23.4) | 15 (20.8) | 7[a] (31.8) | 0.287 |
| Patients (among those with combined therapy) with: | | | | | | | | |
| Azoles | 30[b] (88.2) | 25 (96.2) | 5 (62.5) | 0.033 | 18[c] (81.8) | 14 (93.3) | 4 (57.1) | 0.077 |
| Echinocandins | 3[d] (8.8) | 0 (0.0) | 3 (37.5) | 0.009 | 3[d] (13.6) | 0 (0.0) | 3 (42.9) | 0.022 |
| Amphotericin | 2 (5.9) | 1 (3.8) | 1 (12.5) | 0.421 | 2 (9.1) | 1 (6.7) | 1 (14.3) | 1.000 |
| Length (days) of other antifungals, median ($P_{25}$,$P_{75}$) | 10.0 (8.0, 16.0) | 10.0 (8.0, 14.5) | 14.0 (8.0, 19.0) | 0.709 | 12.0 (7.8, 16.0) | 12.0 (7.8, 15.5) | 11.0 (7.3, 19.3) | 0.963 |

[a]One patient with two additional antifungals; [b]25 patients with fluconazole and 5 patients with voriconazole; [c]15 patients with fluconazole and 3 patients with voriconazole; [d]Two patients with caspofungin and one patient with micafungin

**Table 5** **Outcome. Length of stay and mortality; n (%) except indicated**

| | Total population | | | | Patients with septic shock | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Favorable | Non-favorable | p | Total | Favorable | Non-favorable | p |
| n | 139 | 110 | 29 | | 94 | 72 | 22 | |
| Length (days) of stay in the SICU, median ($P_{25}$,$P_{75}$) | 15.0 (9.0, 30.0) | 15.0 (8.8, 35.0) | 15.0 (8.5, 27.5) | 0.684 | 15.0 (9.8, 29.3) | 16.0 (10.3, 30.0) | 17.5 (8.8, 28.0) | 0.778 |
| Length (days) of hospitalization, median ($P_{25}$,$P_{75}$) | 46.0 (29.0, 75.0) | 53.0 (31.0, 81.0) | 35.0 (15.5, 46.5) | <0.001 | 42.5 (25.8, 76.0) | 52.5 (31.3, 80.0) | 30.5 (14.8, 47.0) | 0.002 |
| Mortality in the SICU | 36 (25.9) | 11 (10.0) | 25 (86.2) | <0.001 | 27 (28.7) | 8 (11.1) | 19 (86.4) | <0.001 |

novelty of the present study reside in its focus on patients with IAC (most of them after major surgery) admitted to surgical ICUs. Apart from describing clinical features of this entity, analysis of patients treated with anidulafungin provided data on the efficacy of this compound.

It has been postulated that severe sepsis/septic shock should alert of the possibility of *Candida* involvement in intraabdominal infections[21]. In our study, the percentage of patients presenting septic shock (67.6%) was higher than the one reported in general ICUs due to ICI (23-38%)[22-24], and this could be related to the surgical ICU setting where the study was performed. In addition, more than 50% patients in the total population and in the subgroup of patients with septic shock presented documented IAC, peritonitis being present in three-quarter of patients. Left untreated, *Candida* may spread within the peritoneal space to distant organs, causing abscesses, multiple organ failure and finally death[21]. Due to this, therapeutic delay in the treatment of *Candida* peritonitis significantly increases mortality, and *Candida* spp. should be covered in any patient with high degree of intraabdominal contamination[21]. In this sense, most patients in our series (75.5%) received anidulafungin as empirical or anticipated therapy. There is no significant benefit of combining antifungals for the treatment of ICI in non-neutropenic patients[3]. Although approximately one-quarter of patients in the present series received combined antifungal therapy, no differences in favorable response were found, regardless the presence of septic shock or not, by comparing patients treated with anidulafungin alone and those concomitantly treated with fluconazole.

*Candida* spp. has been reported as the second most frequent pathogen cultured in peritonitis patients and it has been associated with increased mortality in most studies[11,25], with reported mortality rates between 25% and 60%[11,17]. Mortality rates in the present series were closed to the lower value of this range, even in the subgroup of patients with septic shock.

The involvement of *C. albicans* as predominant species in IAC (65 to 82%) has been reported in European ICUs[26,27]. However, gastrointestinal surgery by itself is a risk factor for acquisition of non-*C. albicans* related infections[17]. In our series, up to 58.2% isolates were *C. albicans*, with *C. glabrata* and *C. krusei* as the most common non-*C. albicans* species. In a previous study in critically ill patients with ICI, *C. albicans* and inadequate antifungal therapy were identified as factors associated with increased mortality[3]. In our study, no significant differences were found by species in clinical response. No specific predictors of mortality have been identified in IAC, and overall prognosis is influenced by site-dependent (extension, origin…) and host-related factors as comorbidities[17]. In accordance with this, in the multivariate analysis, non-favorable response was associated with central nervous or renal system as affected organ/system (SOFA >2) and COPD as underlying condition.

Despite the multicenter design of the study (19 SICUs) and the fact that the present study probably represents the largest series of IAC cases treated with anidulafungin, with a high percentage of patients with septic shock, results should be taken with caution due to the retrospective non-comparative nature of the study. However, the safety profile of anidulafungin in this study with high number of patients with septic shock is valuable and is in accordance with its recognized safe administration to patients with comorbidities and/or concomitant drugs and/or with any degree of renal or hepatic impairment without dose adjustment[28,29], which is important in the treatment of IAC in surgical ICUs.

The results of this study showed that in IAC managed at surgical ICUs, peritonitis was the main presentation, with a high percentage of patients developing septic shock, and with *C. albicans* followed by *C. glabrata* as main responsible species. Anidulafungin treatment in these critically ill patients was mostly empirical followed by anticipated therapy, with a favorable safety profile, even in the subgroup of patients with septic shock.

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## CONFLICT OF INTEREST

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## REFERENCES

1. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012; 18 (Suppl 7):19-37.
2. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:503-35.
3. León C, Ostrosky-Zeichner L, Schuster M. What's new in the clinical and diagnostic management of invasive candidiasis in critically ill patients. Intensive Care Med 2014; 40:808-19.
4. Dimopoulos G, Ntziora F, Rachiotis G, Armaganidis A, Falagas ME. *Candida albicans* versus non-*albicans* intensive care unit-acquired bloodstream infections: differences in risk factors and outcome. Anesth Analg 2008; 106:523-9.
5. De Rosa FG, Motta I, Corcione S, Cattel F, Di Perri G, D'Avolio A. Anidulafungin versus fluconazole: clinical focus on IDSA and ESCMID guidelines. Infez Med 2014; 22:107-11.
6. Ruhnke M, Paiva JA, Meersseman W, Pachl J, Grigoras I, Sganga G, et al. Anidulafungin for the treatment of candidaemia/invasive candidiasis in selected critically ill patients. Clin Microbiol Infect 2012; 18:680-7.
7. Dimopoulos G, Paiva JA, Meersseman W, Pachl J, Grigoras I, Sganga G, et al. Efficacy and safety of anidulafungin in elderly, critically ill patients with invasive *Candida* infections: a post hoc analysis. Int J Antimicrob Agents 2012; 40:521-6.
8. De Rosa FG, Corcione S, Baietto L, Pasero D, Di Perri G, Ranieri VM, et al. Pharmacokinetics of anidulafungin in two critically ill patients with septic shock undergoing CVVH. J Chemother 2013; 25:376-8.
9. Burkhardt O, Kaever V, Burhenne H, Kielstein JT. Extended daily dialysis does not affect the pharmacokinetics of anidulafungin. Int J Antimicrob Agents 2009; 34:282-3.
10. de Ruiter J, Weel J, Manusama E, Kingma WP, van der Voort PH. The epidemiology of intra-abdominal flora in critically ill patients with secondary and tertiary abdominal sepsis. Infection 2009; 37:522-7.
11. Montravers P, Dupont H, Gauzit R, Veber B, Auboyer C, Blin P, et al. *Candida* as a risk factor for mortality in peritonitis. Crit Care Med 2006; 34:646-52.
12. Montravers P, Dupont H, Eggimann P. Intra-abdominal candidiasis: the guidelines-forgotten non-candidemic invasive candidiasis. Intensive Care Med 2013; 39:2226-30.
13. Zaragoza R, Ferrer R, Maseda E, Llinares P, Rodríguez A; EPICO PROJECT GROUP. EPICO 2.0 PROJECT: Development of educational therapeutic recommendations using the DELPHI technique on invasive candidiasis in critically ill adult patients in special situations. Rev Esp Quimioter 2014; 27:196-212.
14. León C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lerma F, et al. A bedside scoring system ("*Candida* score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. Crit Care Med 2006; 34:730-7.
15. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707-10.
16. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270:2957-63.
17. Bassetti M, Marchetti M, Chakrabarti A, Colizza S, Garnacho-Montero J, Kett DH, et al. A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. Intensive Care Med 2013; 39:2092-106.
18. Ullmann AJ, Akova M, Herbrecht R, Viscoli C, Arendrup MC, Arikan-Akdagli S, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect 2012; 18 (Suppl 7):53-67.
19. Ruhnke M, Rickerts V, Cornely OA, Buchheidt D, Glöckner A, Heinz W, et al. Diagnosis and therapy of *Candida* infections: joint recom-

mendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy. Mycoses 2011; 54:279-310.

20. Aguado JM, Ruiz-Camps I, Muñoz P, Mensa J, Almirante B, Vázquez L, et al. Guidelines for the treatment of Invasive Candidiasis and other yeasts. Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). 2010 Update [Article in Spanish]. Enferm Infecc Microbiol Clin 2011; 29:345-61.
21. Hasibeder W, Halabi M. *Candida* peritonitis. Minerva Anestesiol 2014;80:470-81.
22. Bassetti M, Righi E, Ansaldi F, Merelli M, Trucchi C, De Pascale G, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med 2014; 40:839-45.
23. Guzman JA, Tchokonte R, Sobel JD. Septic shock due to candidemia: outcomes and predictors of shock development. J Clin Med Res 2011; 3:65-71.
24. Gutiérrez SM, Heredia M, Gómez E, Gómez JI, Tamayo E. Candidemia in ICU patients with sepsis. Crit Care Med 2013; 41:e385.
25. Hughes MG, Chong TW, Smith RL, Evans HL, Pruett TL, Sawyer RG. Comparison of fungal and nonfungal infections in a broad-based surgical patient population. Surg Infect (Larchmt) 2005; 6:55-64.
26. Dupont H, Paugam-Burtz C, Muller-Serieys C, Fierobe L, Chosidow D, Marmuse JP, et al. Predictive factors of mortality due to polymicrobial peritonitis with *Candida* isolation in peritoneal fluid in critically ill patients. Arch Surg 2002; 137:1341-6.
27. Sandven P, Qvist H, Skovlund E, Gierctsky KE; NORGAS Group and the Norwegian Yeast Study Group. Significance of *Candida* recovered from intraoperative specimens in patients with intra-abdominal perforations. Crit Care Med 2002; 30:541-7.
28. Dowell JA, Stogniew M, Krause D, Damle B. Anidulafungin does not require dosage adjustment in subjects with varying degrees of hepatic or renal impairment. J Clin Pharmacol 2007; 47:461-70.
29. George J, Reboli AC. Anidulafungin: when and how? The clinician's view. Mycoses 2012; 55:36-44.