Efficacy and safety of caspofungin in critically ill patients. ProCAS Study

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ABSTRACT

Introduction. Caspofungin is an echinocandin with proven efficacy in invasive candidiasis (IC) and invasive aspergillosis (IA). ProCAS is a study sponsored by the Working Group of the Infectious Diseases of the Spanish Society of Intensive Care Medicine, which analyzes the effectiveness and safety of caspofungin in routine clinical practice conditions in the critically ill.

Methods. A prospective, multicenter, observational study designed to estimate the clinical effectiveness and safety of caspofungin acetate in the treatment of IC and IA in patients refractory to or intolerant of conventional antifungal therapy. The assessment of effectiveness both clinic and the microbiological was carried out at the end of the treatment with caspofungin.

Results. We included 98 patients, 62 IC proven, 25 probable and 11 IA probable, from 24 centers during 2005 and 2006. Treatment with caspofungin monotherapy was performed in 89.8% of cases and as first line therapy in 54.1%. The favorable clinical response obtained for IC, probable IC, and probable IA was 91.9, 84, and 81.8%, respectively. The microbiological response was favorable in 74.6, 68, and 54.6% for proven cases of IC, probable IC, and probable IA, respectively. No serious adverse effects were observed.

Conclusions. In routine clinical practice conditions, caspofungin is effective and safe for the treatment of invasive fungal infections (IC/IA). The efficacy and safety profile was similar to that observed in published clinical trials.

Keywords: Caspofungin, invasive candidiasis, aspergillosis, critically ill patient, efficacy, safety

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Eficacia y seguridad de caspofungina en el paciente crítico. Estudio ProCAS

RESUMEN

Introducción. Caspofungina es una equinocandina con eficacia probada en candidiasis invasiva (CI) y aspergilosis invasiva (AI). ProCAS es un estudio patrocinado por el Grupo de Trabajo de Enfermedades Infecciosas de la Sociedad Española de Medicina Intensiva Critica Y Unidades Coronarias (Semicyuc), que trata de analizar su efectividad y seguridad en condiciones de práctica clínica habitual en el paciente grave ingresado en UCI.

Material y métodos. Estudio observacional, prospectivo y multicéntrico que tiene como objetivo estimar la efectividad clínica y la seguridad del acetato de caspofungina en el tratamiento de CI y de AI en pacientes críticos refractarios o intolerantes al tratamiento antifúngico convencional. La valoración de la efectividad tanto clínica como la microbiológica se realizó al final del tratamiento con caspofungina.

Resultados. Se incluyeron 98 pacientes; 62 CI probadas, 25 CI probables y 11 AI probables, procedentes de 24 centros, durante los años 2005 y 2006. El tratamiento con caspofungina se realizó en monoterapia en el 89.8% de los casos y como primera línea en el 54.1%. La respuesta clínica favorable obtenida para CI, CI probable y AI probable fue de 91,9%, 84% y 81.8%, respectivamente. La respuesta microbiológica fue favorable en el 74,6%, 68% y 54.6%, para los casos de CI probada, CI probable y AI probable, respectivamente. No se objetivaron efectos adversos graves.

Conclusiones. En condiciones de práctica clínica habitual, caspofungina es eficaz y segura para el tratamiento de infecciones fúngicas invasoras (CI/AI). El perfil de eficacia y seguridad fue similar al observado en los ensayos clínicos publicados.

Palabras clave: Caspofungina, candidiasis invasiva, aspergilosis, paciente crítico, eficacia, seguridad.

INTRODUCTION

Invasive fungal infections represent a significant source of morbidity and mortality in patients admitted to intensive

care units (ICUs). Mortality rates have been reported of up to 70-80% for invasive candidiasis (IC) and 100% for invasive aspergillosis (IA), despite antifungal therapy. Both IC and IA are conditions that are usually diagnosed late, negatively affecting the effectiveness of antifungal therapy.

In Europe, caspofungin is approved for the treatment of IC in adult and pediatric patients, in cases of IA in adult or pediatric patients as rescue therapy or if intolerant to amphotericin B, and as empirical treatment for febrile neutropenic patients with suspected fungal infection (IC/IA).

Caspofungin has broad activity against *Candida* spp and *Aspergillus* spp, and has shown an efficacy similar to fluconazole in the treatment of esophageal candidiasis, to amphotericin B deoxycholate in the treatment of invasive candidiasis, and to liposomal amphotericin B in the empirical antifungal treatment of neutropenic patients.

Invasive fungal infection has an increasing importance in ICUs, with *Candida* spp being the most common fungal isolation, and to a lesser extent, *Aspergillus* spp. The need to reduce the side effects and interactions associated with azoles and the appearance of strains resistant to these drugs led to the development of the echinocandins. Caspofungin was the first approved for the treatment of invasive fungal infections.

In the last update[1] of the clinical practice guidelines for the management of candidiasis of the Infectious Diseases Society of America (IDSA), it is recommended to use echinocandins in case of moderately severe to severe disease, both in neutropenic and non-neutropenic patients, either empirically or as targeted treatment.

There are numerous clinical studies with caspofungin[2-7] that have provided high quality data with a high level of scientific evidence. The need to generate additional information about clinical effectiveness and safety under routine clinical practice conditions justifies the conduct of this study.

MATERIALS AND METHODS

Study population

The study included patients over 18 years of age with a probable or proven diagnosis of IC or IA admitted to intensive care units of Spanish hospitals.

The definitions used in this study of proven, probable, and possible invasive candidiasis and aspergillosis were made in accordance with those adopted by the EORTC/MSG[8].

Patients with IA must be refractory or intolerant to other antifungals; for this purpose, refractoriness is defined as progression of infection or lack of improvement after at least 7 days of prior antifungal therapy, and intolerance as significant toxicity or intolerance developed by the patient during standard antifungal therapy or renal dysfunction (clearance creatinine < 50 mL/min) caused by any other previous condition.

In all patients included, the APACHE II score was calculated within 24 hours of admission to the ICU[9].

Excluded from the study were patients diagnosed based on single positive culture for *Candida* from a single sample (urine, sputum, catheter tip or zone of catheter insertion); patients with osteomyelitis or endocarditis by *Candida* (including infections of prosthetic valves) who have not received adequate surgical treatment before the start of treatment with caspofungin; patients with *Candida* infection of prosthetic material without its removal at the start of treatment with caspofungin; patients with vascular grafts and positive blood cultures for *Candida*; patients with a diagnosis of allergic bronchopulmonary aspergillosis or patients with infection limited to one or more aspergillomas or ocular aspergillosis without adequate surgical treatment before starting treatment with caspofungin. Also were excluded patients with a history of allergy, hypersensitivity or any serious reaction with an antifungal echinocandin or any of the excipients present in the vials of CANCINAS®. Patients with severe hepatic dysfunction (Child-Pugh >9), prognosis of survival less than 5 days, or who had previously participated in this study or any other involving administration of an investigational drug within 14 days prior to admission or during administration of caspofungin, were excluded.

The investigator could exclude patients who had any concomitant disease or condition that could confound the results of the study or create an additional risk to the patient.

Study design

This is a prospective, multicenter, observational study to evaluate the clinical effectiveness and safety of acetate caspofungin in the treatment of invasive *Candida* and *Aspergillus* infections in patients refractory or intolerant to conventional antifungal therapy. In general, the dose of caspofungin was adjusted to the summary of product characteristics, with patients receiving a loading dose of 70 mg IV on the first day of treatment, followed by a maintenance dose of 50 mg/day IV from the second day. In patients with liver dysfunction (Child-Pugh classification A or B), the loading dose was reduced to 35 mg on the first day of treatment.

The study protocol was approved by the ethics committees of the participating sites and informed consent was obtained from patients or their relatives in all cases.

Evaluation of clinical response

The efficacy of caspofungin was evaluated by assessing clinical and microbiological response according to the definitions listed below.

For invasive candidiasis, a complete or partial favorable clinical response was considered as resolution or reduction of signs and symptoms of infection with microbiogical absence of *Candida* infection. An unfavorable clinical response or failure was considered as persistence of signs and symptoms of infection with or without microbiological evidence in the original site or other sterile sites. Clinical relapse was defined as recurrence of signs and symptoms of infection together

with the presence of positive cultures for *Candida* spp or the need to add systemic antifungal therapy as empirical or targeted treatment.

In cases of invasive aspergillosis, complete or partial favorable response was considered as complete or partial resolution or improvement, respectively, of signs and symptoms of infection and radiological or bronchoscopic abnormalities present at the start of treatment with caspofungin. The clinical course was considered as unfavorable (stabilization) in the absence of most signs and symptoms of infection and radiographic or bronchoscopic abnormalities present at the start of the treatment with caspofungin. Unfavorable clinical course (failure) was considered in cases of worsening of signs and symptoms of infection and radiological or bronchoscopic abnormalities present at the start of treatment, requiring starting of alternative antifungal therapy or resulting in patient death. Clinical relapse was defined as the recurrence of IA after treatment discontinuation after the patient had achieved a complete or partial favorable clinical response.

Evaluation of microbiological response

Eradication was considered as negativization of cultures at the end of caspofungin therapy. Microbiological persistence was defined as positive cultures during and at the end of treatment. If a patient suffered clinical and radiological failure and cultures were not available, microbiological response was assessed as persistence. Response was classified as indeterminate when no culture results were available at the end of treatment or other clinical data on which make an assessment of possible microbiological response. If a patient experienced an improvement or clinical stabilization but cultures were not available, microbiological response of the patient was assessed as indeterminate.

Adverse effects

The occurrence of adverse effects described in the summary of product characteristics was monitored: exanthema, angioedema, erythema, pruritus, rash, facial edema, bronchospasm, anaphylaxis, dyspnea, headache, palpitations, tachycardia, nausea, diarrhea, vomiting, phlebitis, arthralgia, and laboratory abnormalities (decrease in hemoglobin, hematocrit, WBC or platelets, hypokalemia, hypocalcemia, metabolic acidosis, increased liver enzymes).

The occurrence of adverse effects was evaluated in two ways. First, the clinical investigators were requested to classify adverse events based on the WHO criteria (WHO toxicity criteria) and to evaluate the implication of caspofungin as the cause of the event, defining each case as "no association", "possible", "probable" or "definite." Second, laboratory parameters were recorded at 3 times during the follow-up: before the start of treatment with caspofungin, at the time of maximum pathological deviation of normal laboratory values during caspofungin therapy and at the end of treatment.

Sample size

This study was designed with no formal hypothesis contrast, and sample size was calculated by estimating a 40% rate of favorable responses for invasive aspergillosis and 63% rate for candidiasis, which is the lower limit of the confidence interval of the response observed as first-line therapy[9].

RESULTS

Patients admitted to intensive care units of 24 Spanish hospitals during 2005 and 2006 were included. Of the 123 patients included, 2 cases were initially excluded because the patients had been treated with the study drug, leaving 121 patients, of which 23 were excluded because they did not meet the inclusion criteria or had incomplete data, so there were 98 patients for the final analysis.

Table 1 shows the demographic characteristics, comorbidities and risk factors of the patients studied. Sixty-two patients had proven *Candida* infection: 44 of these infections were candidemia (6 had associated peritonitis and 1 had associated pleural infection), 14 were peritonitis, and 4 were pleural infections. The study included 25 patients diagnosed with probable infection and 11 with probable diagnosis of aspergilosis (table 2). The different isolates obtained are summarized in table 2 and figure 1.

Treatment

Caspofungin was administered for an average of 14 days (range 9-21). Eighty-eight patients (89.8%) received caspofungin monotherapy and 10 patients (10.2%) received caspofungin in combination with another antifungal therapy. Combination therapy was performed with voriconazole in 6 patients and with fluconazole in 2. Amphotericin B lipid complex (1 patient) and liposomal amphotericin B (1 patient), were also used as combined treatment with caspofungin (table 3).

Clinical effectiveness

In proven cases of candidemia, a favorable complete clinical response was observed in 35 cases (79.5%), a partial clinical response in 6 (13.6%), and clinical failure in 3 (6.8%). When diagnosis was proven non-candidemic invasive candidiasis, the clinical response observed was: a favorable complete response in 14 cases (77.8%), a favorable partial response in 2 (11.1%) and failure in 2 (11.1%).

Clinical response to caspofungin in cases of probable IC was a favorable complete response in 11 patients (44%), a favorable partial response in 10 (40%), and failure in 4 (16%).

In cases diagnosed as probable IA, a complete favorable clinical response was observed in 5 patients (45.4%), a partial favorable clinical response in 4 (36.4%), and stabilization in 2 (18.2%) (table 4). In cases of candidemia, probable IC, and probable IA there were 7 (17.1%), 2 (12.5%), 6 (28.6%) y 2 (22.2%) cases of relapse, respectively.

Table 1 **Demographic characteristics, comorbidities and risk factors of patients studied.**

Demographic data	
Age, median (IQR)	61 (48-71)
Gender	
Male	71 (72.4)
Female	27 (27.6)
Type of patient	
Medical	48 (48.9)
- Oncohematological	11 (11.2)
- Neutropenic	7 (7.1)
Surgical	44 (44.9)
Trauma	6 (6.1)
APACHE II, median (IQR)	15 (10-19)
Surgery requiring admission to ICU	45 (45.9)
Abdominal	36 (80)
Clinical status	
Sepsis	37 (37.7)
Septic shock	31 (31.6)
MOF	15 (15.3)
Comorbidities	
Cardiovascular	40 (40.8)
Respiratory	34 (34.7)
Gastrointestinal	32 (32.6)
Endocrine-metabolic	31 (31.6)
Active cancer	18 (18.4)
Neurological	17 (17.3)
Liver disease	13 (13.3)
Renal disease	10 (10.2)
Risk factors	
Central venous catheter	97 (98.9)
Bladder catheter	94 (95.9)
Mechanical ventilation	82 (83.7)
Arterial catheter	73 (74.5)
Enteral nutrition	59 (60.2)
Total parenteral nutrition	56 (57.1)
Extrarenal filtration	17 (17.3)
Previous antibiotic therapy > 7 days	53 (54.1)
Immunosuppressants	32 (32.6)
Days of pre-ICU admission, median (IQR)	6 (0-23)

ICU: Intensive Care Unit: IQR: Interquartile range, MOF: multiple organ failure, APACHE II: Acute Physiology and Chronic Health Evaluation

Microbiological effectiveness

Microbiological response observed in patients with proven candidemia, according to the definitions above, was eradication in 24 cases (54.5%), presumed eradication in 8 (18.2%), persistence in 9 (20.4%) and indeterminate in 3 (6.8%). In cases of proven non-candidemic IC, microbiological eradication was observed in 8 patients (44.4%), presumed eradication in 7 (38.9%), persistence of positive cultures at the end of caspofungin therapy in 1 (5.5%) and indeterminate in 2 (11.1%).

In cases of probable IC, microbiological eradication was observed in 10 patients (40%), presumed eradication in 7 (28%), persistence in 3 (12%) and indeterminate in 5 (20%).

Regarding the cases included with a diagnosis of probable IA, the microbiological response obtained was eradication in 4 patients (36.4%), presumed eradication in 2 (18.2%), persistence in 3 (27.3%) and indeterminate in 2 (18.2%).

Follow-up

The patients included were followed during their stay in the ICU and after discharge from the ward, with a median of 61 days (range: 1-102). Mortality at 60 days in patients receiving caspofungin was 43.31% (n=42), with a mortality associated with invasive fungal infection of 31%.

Safety

Six adverse events were reported in 6 different patients among the 98 patients included (6.1%). The occurrence of skin exanthema was reported in 5 patients during treatment with caspofungin. No significant changes were seen in the recorded laboratory parameters (AST, ALT, alkaline phosphatase, total bilirubin and creatinine), except in a patient who had mild elevation of direct and total bilirubin. In all cases reported, adverse events were rated as nonserious by investigators and did not require any action.

DISCUSSION

The latest update of the IDSA guidelines[1] on the management of invasive fungal infections (mainly IC), in agreement with the majority opinion of experts, recommend an echinocandin in critically ill patients with severe or suspected disease or confirmation of fungal infection. Oncohematological, neutropenic patients and those with complicated abdominal conditions are the groups with an increased risk of developing IC/IA.

The units participating in the study have a geographic distribution covering most of Spain. Andalusia, Catalonia, and Valencia were communities that provided most patients.

In 25 of the 98 patients, caspofungin therapy was prescribed after failure of initial antifungal treatment with fluconazole. This finding could reflect failure of fluconazole antifungal prophylaxis in high-risk patients, a high rate of infections by fluconazole resistant *Candida* species or an inadequate initial empirical therapy for the clinical condition of the patient.

Of the patients included, 36 (36.7%) had complicated abdominal disease and 31 (31.6%) were in a state of septic shock. Both conditions are one of the main clinical scenarios where invasive *Candida* infection shows a high incidence.

Table 2 Types of fungal infection and isolates.

Type of fungal infection	Number of cases
Proven *Candida* infection	**62**
Candidemia	44
C. albicans	21 (47.7)
Non-*C. albicans*	23 (53.2)
- *C. parapsilosis*	7 (15.9)
- *C. glabrata*	7 (15.9)
- *C. krusei*	3 (6.8)
- *C. tropicalis*	3 (5.8)
- *C. kefyr*	2 (4.5)
- *Candida spp*	1 (2.2)
Peritonitis	14
C. albicans	7 (50)
C. glabrata	5 (35.7)
C. kefyr	1 (7.1)
Candida spp	1 (7.1)
Pleural empyema	4
C. albicans	2 (50)
C. glabrata	1 (25)
C. krusei	1 (25)
Probable *Candida* infection	25
C. albicans	14 (56)
C. tropicalis	2 (8)
C. krusei	2 (8)
C. glabrata	2 (8)
C. lusitaniae	1 (4)
Geotricum candidum	1 (4)
Candida spp	3 (12)
Probable aspergillosis	11
A. fumigatus	5 (45.4)
A. flavus	2 (18)
A. terreus	1 (9.1)
Aspergillus spp	3 (27.2)

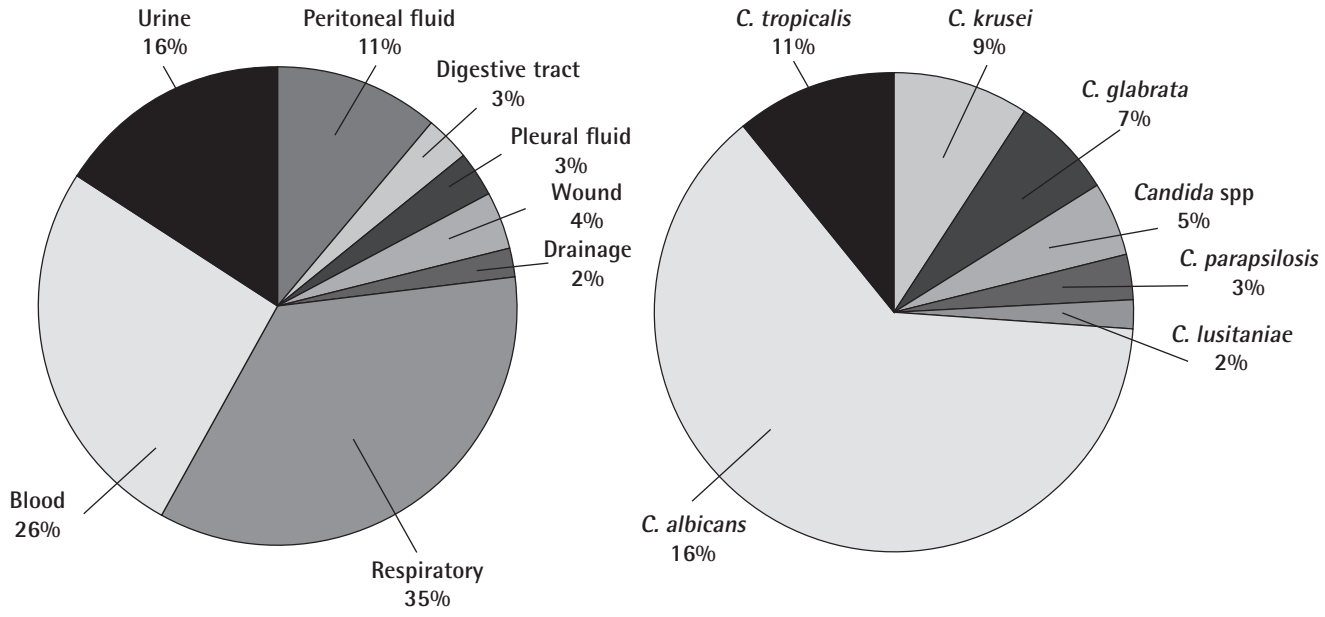

Figure 1 | **Microbiology. Samples and *Candida* species**

When assessing efficacy, the best evidence is obtained from controlled clinical trials. Despite this, observational studies may provide valid results when evaluating clinical response and safety of new drugs, such as caspofungin, from the follow-up of a large number of patients and for sufficient time under routine clinical conditions.

According to the results of this study, caspofungin has been used effectively as first-line treatment and probably as rescue therapy in patients with proven IC, probable IC, and probable IA. The study population was formed by severely ill patients (APACHE II 15 [IQR 10-19]) with associated severe comorbidities. In this group of critically ill patients, a favorable clinical response was obtained in 89.6% (78) of IC (proven + probable) and 81.8%[9] of probable IA. Favorable response rates were higher in patients with proven IC (91.9%) than in patients with probable IC (84%) and probable IA (81.8%). The results are slightly higher to those published by Mora-Duarte et al.[10] (favorable response with caspofungin in 73-81% with IC) and markedly higher than reported by Maschmeyer et al (favorable response in 45% of patients with IA)[11], Maertens et al. (56.4% favorable response)[12] and other authors[2,13,14]. These data have an even greater value considering that in 36% of the cases the indication to start treatment with caspofungin was as rescue for refractoriness to previous antifungal therapy.

Although immunosuppressed patients were not excluded from the study, only 18% of patients included were in this situation at the time of recruitment. This should be considered when analyzing the results obtained in our study.

Table 5 summarizes the characteristics of the clinical trials conducted with caspofungin and response to treatment. Both in immunosuppressed and immunocompetent patients, as preventive or targeted treatment, first-line or rescue therapy, caspofungin has achieved good results in terms of effectiveness and safety.

In our study, *C. albicans* was the most frequently isolated species (63%), and the incidence of infections by non-*C. albicans* was lower than expected given the changes in microbiological characteristics of IC in recent years[15]. As regards the source of isolates, they are similar to those reported in other studies[16].

In the study by Mora-Duarte et al.[10], 42% of patients receiving caspofungin had some adverse effect or laboratory test abnormality, though only in 3 cases (2.6%) was it necessary to discontinue caspofungin therapy.

In critically ill patients, the presence of side effects and drug interactions has greater importance because of the usual coexistence of organ failure and use of a wide range of drugs[20]. The safety profile of caspofungin seen in this and other studies make it be considered one of the antifungal of first-choice in patients with proven or probable IC and as rescue therapy in IA.

This study has some limitations. Since this is an observational study conducted in routine clinical practice, a control group was not used with which to make comparisons, so a superiority or inferiority analysis cannot be performed. In addition, the low number of IA may bias the results. The diagnosis of probable IA and probable CI was performed according to the criterion of the local investigators, which may be associated with a bias due to lack of a uniform diagnostic criterion.

Table 3 Treatment with caspofungin. Types, indication, and rescue.

Type of treatment	Number of cases
Monotherapy	88 (89.8)
Combination therapy	10 (10.2)
Voriconazole	6 (60)
Fluconazole	2 (20)
Amphotericin B lipid complex	1 (10)
Liposomal amphotericin B	1 (10)
Indication	Number of cases
First line	53 (54.1)
Rescue for refractoriness	36 (36.7)
Fluconazole	25 (69.4)
Voriconazole	5 (13.9)
Itraconazole	4 (11.1)
Liposomal amphotericin B	2 (5.5)
Rescue for intolerance	9 (9.2)
Liposomal amphotericin B	3 (33.3)
Fluconazole	2 (22.2)
Amphotericin B lipid complex	2 (22.2)
Voriconazole	2 (22.2)

Table 4 Clinical and microbiological response of caspofungin in the different fungal infections used.

Invasive Candidiasis	Number of cases
Candidemia	44
Clinical response	
Complete	35 (79.5)
Partial	6 (13.6)
Failure	3 (6.8)
Microbiological response	
Eradication	24 (54.5)
Presumptive eradication	8 (18.2)
Persistence	9 (20.4)
Indeterminate	3 (6.8)
Non-candidemic invasive candidiasis*	18
Clinical response	
Complete	14 (77.8)
Partial	2 (11.1)
Failure	2 (11.1)
Microbiological response	
Eradication	8 (44.4)
Presumptive eradication	7 (38.9)
Persistence	1 (5.5)
Indeterminate	2 (11.1)
Probable invasive candidiasis	25
Clinical response	
Complete	11 (44)
Partial	10 (40)
Failure	4 (16)
Microbiological response	
Eradication	10 (40)
Presumptive eradication	7 (28)
Persistence	3 (12)
Indeterminate	5 (20)
Probable invasive aspergillosis	11
Clinical response	
Complete	5 (45.4)
Partial	4 (36.4)
Failure	2 (18.2)
Microbiological response	
Eradication	4 (36.4)
Presumptive eradication	2 (18.2)
Persistence	3 (27.3)
Indeterminate	2 (18.2)

*** Includes patients with abdominal candidiasis (peritonitis), and pleural empyema.**
n (%): number of cases, percentage

Table 5 Description of characteristics of the clinical trials conducted with caspofungin.

Study	Patient type	Outcome
Marr, 2004[17]	IA: Voriconazole + Caspofungin vs Voriconazole	Decreased mortality after 3 months. OR: 0.28 (0.28-0.92). p=0.011
Betts, 2009[18]	IC: Caspofungin (standard dose) vs Caspofungin 150 mg/day	Favorable response: 71.6% vs 77.9%
Winkler, 2010[6]	IC + IA: SOT recipient	Favorable response: IC 89%. IA 74%.
Petrovic, 2007[19]	IC + IA: SOT recipient	Favorable response: IC 83%. IA 50%.
Cornely, 2007[20]	IC without candidemia	Favorable response: 81%.
Glasmacher, 2006[21]	Immunosuppressed: Probable or proven fungal infection	Favorable response: IC 62%. IA 49%. Survival 30 days 70%.
Anttila, 2007[2]	IC + IA	Favorable response: IC 78%. IA 50%.
Walsh, 2004[22]	Neutropenic. Empirical ATF (Caspofungin vs Liposomal Amphotericin B)	Favorable response: CAS 33.9%. LAFB 33.7%.
Sipsas, 2009[3]	Oncologic with candidemia	Clinical response 78%. Microbiological response 77%. Overall mortality at 30 days: 21%.
Senn, 2009[5]	Post-abdominal surgery with high risk of IC	Efficacy of preventive treatment: 95%.

IA: invasive aspergillosis, IC: invasive candidiasis, OR: Odds ratio; SOT: solid organ transplant, ATF: antifungal, CAS: Caspofungin, LAFB: Liposomal amphotericin B

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