Caspofungin treatment in severely ill, immunocompromised patients: a case-documentation study of 118 patients


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Background: Caspofungin has shown efficacy in empirical antifungal therapy in neutropenic patients, refractory invasive Aspergillus infections and invasive candidiasis. Here we report the currently largest series of patients treated with caspofungin outside clinical trials.

Methods: Centres in Germany that were known to treat patients with invasive fungal infections were asked to fill out detailed questionnaires for all patients treated with caspofungin. No effort was made to influence the decision to use caspofungin.

Results: A total of 118 patients were evaluable (median age 48 years, interquartile range 38–58), out of which 41 (35%) suffered from acute leukaemia, 31 (26%) had allogeneic stem cell transplants, 16 (14%) lymphoma or myeloma, 8 (7%) autologous stem cell transplants and 22 (19%) other causes for immunosuppression. One hundred and six patients were evaluable for efficacy out of which 68 (64%) patients achieved a complete or partial remission. A total of 81 out of 115 (70%) patients were alive 30 days after the end of caspofungin therapy. Response rates were similar in proven (20/32, 63%) and probable (27/46, 59%) infections, in neutropenic patients (41/55, 75%) and in patients who were (44/70, 63%) or were not (24/36, 67%) refractory to antifungal pre-treatment. The response rate in mechanically ventilated patients was 29% (7/24). Caspofungin was well tolerated, even in 14 patients, who were concomitantly treated with ciclosporin A, no drug-related elevations of bilirubin, alanine aminotransferase or creatinine were found.

Conclusions: This open case study of severely ill patients with invasive fungal infections demonstrates both excellent efficacy and very low toxicity of caspofungin.

Keywords: fungal infections, candidiasis, aspergillosis, safety

Introduction

Caspofungin is the first-in-class echinocandin antifungal with a broad spectrum of activity, Candida and Aspergillus spp., and an excellent tolerability.1,2 It has been successfully investigated and licensed in the United States and in Europe for refractory invasive Aspergillus infections,3 invasive Candida infections4 and empirical antifungal therapy in neutropenic patients.3 Still, our understand...
standing of its efficacy and tolerability outside of clinical trials and especially in those severely ill patients, usually excluded from clinical trials, as well as neutropenic patients with invasive fungal infections is limited.

In order to collect more data on the efficacy and tolerability from these populations an open case documentation was carried out in Germany. Major treatment centres reported on their experience with caspofungin before and shortly after licensing of the drug in Europe. A particular focus was placed on safety of caspofungin, given that previously unstudied patient populations were included.

Patients and methods

In spring and summer 2001 tertiary treatment centres in Germany were contacted and invited to document patients treated with caspofungin in their institutions from June 2001 to January 2003. There were no inclusion or exclusion criteria. However, to avoid duplicate reporting, patients should not have received caspofungin as part of a clinical trial. Centres were asked to retrospectively or prospectively report data for consecutive patient groups and avoid patient selection according to response. They were provided with a 20-page structured questionnaire that had been developed and tested by the University clinics of Frankfurt and Bonn. The criteria for diagnosis were based on the 1999 version of the EORTC/MSG criteria.6

Predefined response criteria were used in the questionnaire: complete remission (CR), complete disappearance of all clinical, radiological and microbiological signs of the fungal infection; partial remission (PR), disappearance of all clinical and microbiological signs of the fungal infection, but with radiological residuals. Response was defined as CR or PR. Stable disease and progressive disease were defined as no change or progression of fungal infection-related signs. Success was assessed at the end of therapy. Adverse events, graded according to the WHO criteria, were evaluated with detailed list and treatment-related changes in important biochemical parameters and were assessed by comparing values at three time points: before start of caspofungin, the maximum abnormal results during therapy with caspofungin and at the end of caspofungin treatment. The last two values could be the same as a result of treatment discontinuation due to toxicity. Normal distribution for these parameters was not assumed. Initially, all variables were assessed all together with the Friedman test for k dependent variables. Pairs of each variable were compared with the Wilcoxon test for two dependent variables only if a statistically significant result was obtained in the overall test.

Data quality was assured by screening all documentation forms for missing or contradictory data and sending queries to the investigating physicians. Then, all response evaluations by the treating physicians were re-evaluated by the study coordinators. Patients were designated as non-evaluable for response if no evidence of a fungal aetiology of the infectious episode was seen in the retrospective evaluation of all available data. This occurred in five patients who had received allogeneic stem cell transplantation. Eighteen of the patients who had received allogeneic transplants suffered from graft-versus-host disease (GVHD; acute 12, chronic 6, grade III/IV 6). Among the transplanted patients 15 suffered from acute myeloid leukaemia, 4 each from chronic myeloid leukaemia, lymphoma or multiple myeloma, 3 from acute lymphoblastic leukaemia and 1 from aplastic anaemia. Medical immunosuppression, AIDS or major surgery was noted in five patients each (4%). Two patients (2%) were treated after solid organ transplantation, and five (4%) had other underlying diseases.

Chemotherapy had been given to 89 (75%) patients (standard dose 62%, high-dose 38%; anthracyclines 55%, cytarabine 54%, cyclophosphamide 25%, etoposide 23%, methotrexate 17%). Twenty-three patients (20%) received corticosteroids, 14 (12%) ciclosporin A, 6 (5%) mycophenolate and 2 tacrolimus. Thirty-four patients (29%) were in an intensive care ward at the start of caspofungin therapy and 29 (25%) were on mechanical ventilation.

Clinical and microbiological findings

According to the EORTC/MSG criteria, 35 patients (30%) had a proven infection; 21 of these infections were located in the lung, 5 were disseminated and 5 other infections were located in the peritoneum (2), the eye, the liver and the urinary tract (1 each). Four infections were restricted to the oesophagus. A total of 15 of the 35 proven infections were caused by Aspergillus spp., and in two patients unspecified Hyphomycetes were reported.

Candida albicans was isolated in four, Candida glabrata in five, Candida krusei in four and other Candida spp. in four patients. Rhodotorula glutinis was isolated in one patient who responded completely to caspofungin monotherapy. Six of these patients suffered from fungaemia and four from Candida oesophagitis (all four responded, but were excluded from efficacy analysis).

According to the EORTC/MSG 1999 criteria6 51 patients had a probable invasive fungal infection and 32 had a possible invasive
fungal infection (including patients who received empirical antifungal therapy).

**Antifungal therapy before caspofungin**

Ninety-six (81%) patients had received other systemic antifungal therapy before treatment with caspofungin. For 15 (16%) patients in this group the previous treatment was prophylactic, 55 (57%) patients had received prior treatment as treatment for a fungal infection and 26 (27%) patients had received prophylactic as well as therapeutic antifungal therapy before caspofungin.

Sixty-two (65%) of those with an antifungal treatment patients had received conventional amphotericin B, 48 (50%) itraconazole, 23 (24%) fluconazole, 18 (19%) liposomal amphotericin B and 7 (7%) other drugs. The doses were usually adequate for prophylaxis or therapy (data not shown).

Treating physicians reported that the principle reason for starting caspofungin therapy was failure of the previous antifungal treatment in 67 (70%) patients, in 17 (18%) patients initiation of caspofungin was due to patient intolerance of the previous therapy and for 12 (13%) patients previous therapy was changed for both efficacy and tolerability considerations. In total, 79 patients were considered refractory to the previous treatment.

The previous antifungal treatment was administered for a median of 19 days (IQR 10–39 days); 38 (32%) patients had received two and 11 (9%) patients three or more systemic antifungals before caspofungin.

**Caspofungin administration**

Caspofungin was administered for a median of 15 days (range 2–217, IQR 11–26 days). The total number of treatment days was 2893. The dosages used varied (50 mg/day, 25%; 70 mg/day then 50 mg/day, 44%; 70 mg/day, 18%; 100 mg/day then 50 mg/day, 10%; 100 mg/day, 3%; 120 mg/day then 50 mg/day, 1%); the reasons for not using the recommended doses (70 mg on day 1 and 50 mg thereafter in patients with <80 kg body weight) were not completely elucidated. However, one consideration might be that in summer 2001, 70 mg vials were not available in several institutions.

Ninety-four (80%) patients received monotherapy with caspofungin and 24 (20%) patients received one or more additional antifungal agent in combination with caspofungin. In 14 of these 24 patients amphotericin B deoxycholate was administered while liposomal amphotericin B was co-administered in 10 patients. Itraconazole (4 patients), voriconazole (2), fluconazole (2) and flucytosine (1) were also administered with caspofungin.

**Efficacy**

**Overall survival.** Twenty-one patients (18%) died during therapy with caspofungin and 13 patients (11%) died within 30 days after the end of caspofungin therapy. Survival information was not available for three patients, who were discharged shortly after the end of therapy. Eighty-one (70%) of the 115 patients were still alive 30 days after the end of therapy with caspofungin.

**Efficacy population.** Twelve patients were excluded from the efficacy analysis. In two patients the response to treatment with caspofungin was not evaluable (i.e. incomplete or contradictory documentation not resolved by contact with documenting physicians). Six patients, who all had received empirical antifungal therapy, had no fungal infection in the evaluation at the end of therapy and four patients with Candida oesophagitis (all had responded) were excluded to restrict the efficacy analysis to invasive fungal infections. Therefore, efficacy was analysed in 106 patients. The baseline characteristics of patients excluded from the efficacy analysis did not differ from the remaining group with the exception of the body weight which was significantly lower in the excluded patients.

**Response rates.** According to predefined criteria, a CR was achieved in 9/106 (8%), 59 (56%) achieved a PR and 5 (5%) patients showed no change of their disease status. Thirty-three (31%) patients were progressive despite therapy with caspofungin. The overall response rate (CR + PR) was 64% (68/106).

Using the 1999 EORTC/MSG criteria, a complete or partial response was observed in 20 of 32 evaluable patients with a proven invasive fungal infection (63%), 27 of 46 patients with a probable invasive fungal infection (59%) and 21 of 28 patients with a possible invasive fungal infection (75%) (Table 1).

Eight of fourteen evaluable patients with proven invasive Candida infections responded (57%). Three of these were classified as a partial response by the investigating physician for unclear reasons. One of these patients did not receive any antifungal medication after successful treatment with caspofungin and two others received continued oral treatment with fluconazole or voriconazole.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N</th>
<th>CR [ % (n)]</th>
<th>PR [ % (n)]</th>
<th>SD [ % (n)]</th>
<th>PD [ % (n)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven invasive fungal infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus fumigatus</em></td>
<td>15</td>
<td>7 (1)</td>
<td>60 (9)</td>
<td>0 (0)</td>
<td>33 (5)</td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>14</td>
<td>36 (5)</td>
<td>21 (3)</td>
<td>7 (1)</td>
<td>36 (5)</td>
</tr>
<tr>
<td>other fungi</td>
<td>3</td>
<td>67 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>33 (1)</td>
</tr>
<tr>
<td>No pathogen isolated</td>
<td>46</td>
<td>0 (0)</td>
<td>59 (27)</td>
<td>4 (2)</td>
<td>37 (17)</td>
</tr>
<tr>
<td>possible IFI</td>
<td>28</td>
<td>4 (1)</td>
<td>71 (20)</td>
<td>7 (2)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>8 (9)</td>
<td>56 (59)</td>
<td>5 (5)</td>
<td>31 (33)</td>
</tr>
</tbody>
</table>

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; IFI, invasive fungal infection.

*These include *C. albicans* (CR + PR 2/3), *C. krusei* (1/4), *C. glabrata* (3/4), *C. albicans* and *C. glabrata* (1/1), *Candida* spp. (1/2).

*These include *R. glutinis* (1/1) and *Hyphomycetes* (1/2).
after severe and disseminated Candida infections. Out of 32 evaluable patients, 23 with proven or probable invasive Aspergillus infections (72%) responded to therapy with caspofungin. Ten of fifteen patients (67%) with proven invasive Aspergillus infections responded (CR 1, PR 9) (Table 1).

We analysed the response also according to the dose of caspofungin. Twenty evaluable patients received a dose clearly above the recommend dose (70 mg/day throughout or higher), their response rate was, however, comparable to that of the remaining patients (60% versus 65%).

Six of sixty-eight (9%) patients who had achieved a CR or PR died within 30 days of the end of caspofungin therapy from causes unrelated to invasive fungal infections; progressive malignancy (3), GVHD (1), CNS bleeding (1) and pulmonary embolism (1). One of five patients with stable disease died within this time period and 25/33 (76%) patients with progressive invasive fungal infection.

Seventy of eighty-seven (80%) evaluable patients who had received prior antifungals were switched to caspofungin due to insufficient efficacy of the previous antifungal therapy and 44 (63%) of these patients responded. Of 17 patients who were treated with caspofungin due to intolerance of the previous antifungal 12 (71%) responded and 12 of 19 patients (63%) who received caspofungin as first-line therapy achieved a CR or PR (Table 2). Eighty-three evaluable patients were treated with caspofungin monotherapy and 55 achieved a response (66%). Thirteen of twenty-three evaluable patients with combination antifungal therapy achieved a response (57%). Baseline and disease characteristics were not significantly different between patients receiving mono- or combination therapy.

Analysis according to patient subgroups. Efficacy was evaluated in different subgroups of patients (Figure 1). Patients with haematological malignancies (acute leukaemia, lymphoproliferative malignancies, autologous stem cell transplantation) responded in 41 of 60 evaluable cases (68%), 17 of 29 evaluable patients after allogeneic stem cell transplantation responded (59%) and 10 of 17 evaluable patients with other conditions responded (59%) (Table 2).

Patients on mechanical ventilation. Twenty-nine patients (25%) started caspofungin therapy while being treated with mechanical ventilation in a critical care unit. Twenty-four of these were evaluable (reason for non-evaluation in the five patients: no invasive fungal infection in retrospective evaluation in three patients and insufficient documentation in two). Of these, 9 were suffering from a haematological malignancy (acute leukaemia 5, lymphoma 4), 5 had received an allogeneic stem cell transplant and 10 had other underlying diseases (of these, 4 patients after extensive surgery, 1 patient with a kidney/pancreas graft). Eight of these patients were neutropenic, 11 received haemodialysis or haemofiltration therapy. Invasive fungal infections were proven in 10 patients (Aspergillus fumigatus in 3, Candida spp. in 7) and probable in 13. Of these, 12 patients died during the therapy with caspofungin, and 7 of the 24 evaluable patients responded (6 CR and 1 PR) (29%). Six patients survived for >30 days after the end of caspofungin therapy.

Fifty-nine patients were neutropenic (<0.5 G/L) when the invasive fungal infection was diagnosed. The mean duration of neutropenia was 19 days (IQR 11–26 days). Twenty-five patients (21%) were severely neutropenic with a neutrophil count ≤0.1 G/L at start of caspofungin therapy and 36 (31%) were severely neutropenic during this therapy. Fifty-five patients were evaluable for response and 41 of these responded (75%) (Table 2). Thirty-nine patients were neutropenic at the start of therapy with caspofungin; of these 36 were evaluable and 25 responded (69%). Proven or probable invasive fungal infections were seen in 26 neutropenic patients and 16 responded (62%). Fourteen evaluable patients were still neutropenic at the end of the therapy with caspofungin and seven of these responded (50%).

Table 2. Number of evaluable patients (N) and response rates [RRs, % (n/N)] cross-tabulated by different patient subgroups

<table>
<thead>
<tr>
<th>RR by probability of invasive fungal infection</th>
<th>N</th>
<th>proven [% (n/N)]</th>
<th>probable [% (n/N)]</th>
<th>possible [% (n/N)]</th>
<th>total [% (n/N)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous antifungal therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>19</td>
<td>60 (3/5)</td>
<td>67 (4/6)</td>
<td>63 (5/8)</td>
<td>63 (12/19)</td>
</tr>
<tr>
<td>intolerant</td>
<td>17</td>
<td>100 (1/1)</td>
<td>58 (7/12)</td>
<td>100 (4/4)</td>
<td>71 (12/17)</td>
</tr>
<tr>
<td>refractory</td>
<td>70</td>
<td>62 (16/26)</td>
<td>57 (16/28)</td>
<td>75 (12/16)</td>
<td>63 (44/70)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute leukaemia, lymphoproliferative malignancies, autologous SCT</td>
<td>60</td>
<td>65 (11/17)</td>
<td>63 (19/30)</td>
<td>85 (11/13)</td>
<td>68 (41/60)</td>
</tr>
<tr>
<td>allogeneic SCT</td>
<td>29</td>
<td>57 (4/7)</td>
<td>50 (5/10)</td>
<td>67 (8/12)</td>
<td>59 (17/29)</td>
</tr>
<tr>
<td>other conditions</td>
<td>17</td>
<td>63 (5/8)</td>
<td>50 (3/6)</td>
<td>67 (2/3)</td>
<td>59 (10/17)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not neutropenic at diagnosis of IFI</td>
<td>51</td>
<td>71 (12/17)</td>
<td>48 (9/19)</td>
<td>40 (6/15)</td>
<td>53 (27/51)</td>
</tr>
<tr>
<td>neutropenic at diagnosis of IFI</td>
<td>55</td>
<td>53 (8/15)</td>
<td>72 (18/25)</td>
<td>100 (15/15)</td>
<td>75 (41/55)</td>
</tr>
<tr>
<td>neutropenic, start of caspofungin</td>
<td>36</td>
<td>50 (4/8)</td>
<td>67 (12/18)</td>
<td>90 (9/10)</td>
<td>69 (25/36)</td>
</tr>
<tr>
<td>neutropenic, end of caspofungin</td>
<td>14</td>
<td>0 (0/3)</td>
<td>43 (3/7)</td>
<td>100 (4/4)</td>
<td>50 (7/14)</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>63 (20/32)</td>
<td>59 (27/46)</td>
<td>75 (21/28)</td>
<td>64 (68/106)</td>
</tr>
</tbody>
</table>

RR, response rate (CR + PR); n, number of responding patients; N, total number of patients; SCT, stem cell transplantation; IFI, invasive fungal infection.
Adverse events

Adverse events were assessed in two ways. First, the investigating physician was asked to grade adverse events on a comprehensive list according to the WHO toxicity criteria and to assess the probability of a causative role of caspofungin for each event (none, possible, probable and definite). Second, important biochemical parameters were collected at three time points: before start of caspofungin, the maximum pathological deviation during therapy with caspofungin and at the end of caspofungin treatment.

In total, WHO grade III/IV adverse events occurred in 40 of the 118 patients; none of these was considered to be related to caspofungin. The following WHO grade II adverse events were probably related to caspofungin: rigor during infusion (n = 1), skin reaction (erythema) (n = 1), diarrhoea (n = 3), nausea (n = 2). In one patient a WHO grade I skin reaction was considered to be definitely related to caspofungin.

Serum concentrations of selected biochemical parameters [creatinine, serum potassium, total serum protein, total bilirubin, γ glutamyl transferase (γGT), alanine aminotransferase (ALT) and lactate dehydrogenase] were significantly different when all three analysed time points (before caspofungin therapy, maximum concentration during caspofungin therapy and at the end of therapy) were compared in the Friedman test. Additional pairwise testing revealed that there were statistically significant differences in all the variables between start and maximum pathological deviation during therapy. However, only γGT revealed significant differences between the start and end of therapy with caspofungin. The γGT was 56 U/L (IQR 28–139) at start, 114 U/L (36–215) at maximum and 74 U/L (27–185) at the end of therapy with caspofungin (P < 0.001 for overall comparison, P = 0.032 for start versus end).

Co-administration of ciclosporin A. When changes in these biochemical parameters were analysed according to the use of ciclosporin A as co-medication the results were equivalent with all variables showing significant differences in the overall comparison of all three time points and no differences between start and end. γGT was not statistically different within the group without ciclosporin A (P = 0.069 for start versus end of caspofungin therapy) and in the group with ciclosporin A (P = 0.539 for start versus end). Notably, there were no statistical differences between start and end of caspofungin therapy for ALT (P = 0.210 and P = 0.633 for patients with and without ciclosporin A). These results are shown in Figures 2 and 3. No discontinuations of either caspofungin or ciclosporin A for toxicity reasons were reported.

Sensitivity analysis

To unmask a potential selection bias we analysed the response rates from centres according to the number of patients reported. Seven centres reported a total of 16 evaluable patients (1–5 each) with a response rate of 75% (95% CI 51–90). Another seven centres reported a total of 60 evaluable patients (6–10 each) with a response rate of 60% (95% CI 47–71%) and one centre reported 30 evaluable patients with a response rate of 67% (95% CI 49–81%) (χ² test for trend, P = 0.758).
Discussion

This study reports the efficacy and safety of caspofungin in a large unselected population of patients with invasive fungal infections in Germany. To our knowledge, it is the largest report of a case series outside the clinical trials programme of the manufacturer. The response rate of 64% and the 70% survival rate 30 days after the end of therapy represent very good evidence of caspofungin’s efficacy in this seriously ill population. This degree of efficacy is demonstrated throughout the various subgroups of the study population analysed (proven and probable infections due to Aspergillus spp. or Candida spp., neutropenic patients, patients with different
underlying diseases and patients on mechanical ventilation at the start of caspofungin therapy). Remarkably, 63% of those patients who were refractory to mostly extensive previous antifungal therapy responded to caspofungin.

Similarly, the safety profile of caspofungin was excellent. No grade III or IV adverse event according to the WHO toxicity grading was considered to be at least probably related to caspofungin; the number of recorded events matches the rate expected in a comparable patient population. Only a few drug-related grade I and II events were noted (seven patients in total, infusion and skin reactions, diarrhoea and nausea).

A further finding which is of particular clinical relevance is the lack of drug-related toxicity in patients who received both ciclosporin A and caspofungin. In a Phase I study mild transient ALT elevation had occurred in 5 of 12 healthy subjects after 1 day of caspofungin and ciclosporin A. However, the results of our study are in line with several other reports (two full papers7,8 and two abstracts9,10) which demonstrate no harmful interaction of ciclosporin A and caspofungin in severely ill patients mostly after allogeneic stem cell transplantation. Therefore, a cautious recommendation can be made that the concomitant application of caspofungin and ciclosporin A is not harmful and that caspofungin can be considered in patients receiving ciclosporin A. Clearly, close monitoring of hepatic function is advisable for many reasons in this group of patients.

The prognosis of patients with invasive fungal infections on mechanical ventilation is generally very poor.11–13 In this study, 29 patients were on a mechanical ventilator at the start of caspofungin. Seven of twenty-four (29%) evaluable patients responded and six responders survived for >30 days after the end of caspofungin.

The experience with caspofungin in neutropenic patients with proven or probable infections is still limited and as such, this caspofungin. Seven of twenty-four (29%) evaluable patients responded and six responders survived for >30 days after the end of caspofungin.

Table 3 summarizes our experience for invasive fungal infections.17

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Response (CR + PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Candida infection protocol #14/24/25/2615,16</td>
<td>29</td>
<td>18 (62%)</td>
</tr>
<tr>
<td>German case documentationa</td>
<td>5</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>total Candida</td>
<td>34</td>
<td>21 (62%) 95% CI: 45–76%</td>
</tr>
<tr>
<td>Invasive Aspergillus infections protocol #19/24/25/2615,16</td>
<td>46</td>
<td>16 (35%)</td>
</tr>
<tr>
<td>German case documentationa</td>
<td>19</td>
<td>16 (84%)</td>
</tr>
<tr>
<td>total Aspergillus</td>
<td>65</td>
<td>32 (49%) 95% CI: 38–61%</td>
</tr>
</tbody>
</table>

*aPre-treated.

In conclusion, this large open case-documentation demonstrates very good antifungal activity and no severe drug-related toxicity in severely ill patients, including neutropenic patients or patients on mechanical ventilation. The results of this study clearly help to increase our confidence in caspofungin and its role in the management of systemic fungal infections.

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