# Impact of echinocandin on prognosis of proven invasive candidiasis in ICU: a post-hoc causal inference model using the AMARCAND2 study

Sébastien Bailly, Olivier Leroy, Elie Azoulay, Philippe Montravers, Jean-Michel Constantin, Hervé Dupont, Didier Guillemot, Olivier Lortholary, Jean-Paul Mira, Pierre-François Perrigault, et al.

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Authors: Sébastien Bailly[1], Olivier Leroy[2], Elie Azoulay[3], Philippe Montravers[4], Jean-Michel Constantin[5], Hervé Dupont[6], Didier Guillemot[7], Olivier Lortholary[8], Jean-Paul Mira[9], Pierre-François Perrigault[10], Jean-Pierre Gangneux[11], Jean-François Timsit[1,12]

Running title: Prognosis of ICU patients treated with echinocandin

1 - Inserm UMR 1137 - IAME Team 5 – DeSCID : Decision SCiences in Infectious Diseases, control and care INSERM/ Paris Diderot, Sorbonne Paris Cité University, Paris, France

2 - Medical ICU, Chatiliez Hospital, Tourcoing, France.

3 - Medical ICU, Saint-Louis University Hospital, Paris, France.

4 - Paris Diderot Sorbonne Cite University, and Anesthesiology and Critical Care Medicine, Bichat-Claude Bernard University Hospital, APHP, Paris France

5 - Perioperative Medicine department, Clermont-Ferrand University Hospital, Clermont-Ferrand, France.

6 - Surgical ICU, Amiens University Hospital, Amiens, France.

7 – Inserm UMR 1181 « Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases » (B2PHI), F-75015 Paris, France

8 - University Paris Descartes, Necker Pasteur Center for Infectious Diseases, Necker Enfants-Malades Hospital, IHU Imagine, Paris; and Pasteur Institute, National Reference Center for Invasive Mycoses and Antifungals, CNRS URA3012, Paris, France.

9 - Medical ICU, Cochin University Hospital, APHP, and Paris Descartes, Sorbonne Paris Cité University, Paris, France

10 - Medical-surgical ICU, Montpellier University Hospital, Montpellier, France.

11 - Mycology, Rennes University Hospital, Rennes, France.

13 - Medical ICU, Paris Diderot University/Bichat University Hospital, APHP, Paris, France.

Highlights

- 397 ICU patients with proven invasive candidiasis,
- Treatment with azoles or echinocandins
- Echinocandins were more frequently administered to severely ill patients
- After adjustment, echinocandin use not associated with an improved 28-day prognosis
- A marginal beneficial effect of echinocandins for patients with concomitant septic shock.

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Abstract

Objective: guidelines recommend first-line systemic antifungal treatment (SAT) with echinocandins in invasive candidiasis (IC), especially in critically ill patients. This study aimed at assessing the impact of echinocandins compared to azoles as initial SAT on the 28-day prognosis in adult ICU patients.

Methods: From the prospective multicenter AmarCAND2 cohort (835 patients), we selected those with documented IC and treated with echinocandins (ECH) or azoles (AZO). The average causal effect of echinocandins on 28-day mortality was assessed using an inverse probability of treatment weight (IPTW) estimator.

Results: 397 patients were selected, treated with echinocandins (242 patients, 61%) or azoles (155 patients, 39%); septic shock: 179 patients (45%). The median SAPSII was higher in the ECH group (48 [35;62] vs. 43 [31;58], p=0.01). Crude mortality was 34% (ECH group) vs. 25% (AZO group). After adjustment on baseline confounders, no significant association emerged between initial SAT with echinocandins and 28-day mortality (HR: 0.90; 95%CI: [0.57;1.41]; p=0.75). However, echinocandin tended to benefit patients with septic shock (HR: 0.46 [0.19;1.07]; p=0.07).

Conclusion: Patients who received echinocandins were more severely ill. Echinocandin use was associated with a non-significant 7% decrease of 28-day mortality and a trend to a beneficial effect for patient with septic shock.

Introduction

Invasive candidiasis (IC) are known to be a leading cause of nosocomial infection, particularly in intensive care units (ICUs). Over the twenty past years, new antifungal drugs were approved for the treatment of IC, particularly azoles and echinocandins which have been shown to be better tolerated. Moreover, echinocandins have an extended spectrum for *Candida* species, including *Candida glabrata* and *Candida krusei* for which azole agents are known to be less sensitive. The emergence of this new class of antifungal agents had changed the way of managing IC and new guidelines were issued that recommend to prescribe echinocandins as first line antifungal therapy and to consider fluconazole only as an alternative for patients who are not critically ill [1, 2].

However, despite of these developments, the incidence and the mortality of IC remained unchanged over the past years [3, 4] and raise the question about the efficacy of these recommendations. Moreover, it was shown that antifungal therapy clearly impacts the distribution and the susceptibility of *Candida* species in an ICU [5, 6], induces a selection of the resistant strains possibly responsible for clinical failure [7] and leads to costs increase [8].

Two trials demonstrated that echinocandins are as effective as amphotericin B [9, 10], but there are poor data on the comparison of echinocandins and azoles in the case of ICU patients.

In a randomized, double blind, non inferiority trial included 245 patients, Reboli *et al* showed that anidulafungin was non inferior to fluconazole in the treatment of IC [11]. In a secondary analysis of the same randomized clinical trial, which included a subgroup of 163 critically ill patients, Kett *et al* showed that anidulafungin had a better global response rate (70.8% N=89) at the end of treatment than fluconazole (54.1% N=74), but without any effect of anidulafungin on survival [12]. Further comparisons between azoles and echinocandins in the most severely ill ICU patients with proven candidemia are lacking.

This explains why the last IDSA guidelines recommend echinocandins as the preferred empiric therapy in non-neutropenic ICU patients, but still consider fluconazole only as an acceptable alternative for patients without recent exposure to azoles and who are not colonized with azole-resistant *Candida* species [1].

From the prospective multicenter AmarCAND2 cohort, i.e., ICU patients treated by systemic antifungal therapy (SAT) for suspected or documented IC, we selected the subset of patients with documented invasive candidiasis and treated with azoles or with echinocandins in order to assess whether echinocandins, compared to azoles, are beneficial for the 28-day patient prognosis. We used inverse probability of treatment weighted (IPTW) estimator to adjust on probability of being treated with echinocandins.

Material and Method

**Study design**

The patients were selected from a multicenter, prospective, observational study conducted in French intensive care units (ICUs) during one year (2012-2013): AmarCAND2. The investigating centers were ICUs having managed at least one IC within the past year, and willing to participate into the study. Investigators enrolled patients according to the study protocol and managed them according to their own clinical judgment, independently from the sponsor. The Ethics Committee of the French Intensive Care Society and the French National Committee for Data Protection and Freedom of Information approved the study. Such an observational study does not require patients to sign an informed consent according to French regulations; however, written information was provided and oral consent was obtained from all participating patients whenever possible, or their family.

**Patients**

Investigators enrolled consecutive adult patients hospitalized in ICU and requiring SAT for documented or suspected invasive *Candida* infection during their ICU stay. Patients receiving prophylactic SAT, those with neutropenia (absolute neutrophil cell count $\leq 500/mm^3$), those who had undergone solid organ transplant within the previous 15 days or those receiving SAT for a mold infection were excluded. Clinical and mycological data collected were defined elsewhere [13, 14].

**Studied population**

AmarCAND2 patients with a primarily or secondarily documented IC were included in the study. Patients with another initial SAT than echinocandins (caspofungin, micafungin or anidulafungin) or azoles (fluconazole or voriconazole) and patients who received SAT for a

suspected not secondarily documented IC were excluded. Patients were divided into two groups according to the initial SAT: 1) Echinocandins group (ECH) and 2) Azoles group (AZO).

**Study outcomes**

The primary outcome was to evaluate whether echinocandins treatment as initial SAT was, or not, associated with the improvement of the 28-day mortality as compared to the mortality of adult non-neutropenic ICU patients who received azoles as initial SAT. Sub-group analyses of the primary objective were performed for (1) by considering only patients with an inadequate loading dose of fluconazole (<12 mg/kg) (2) patient with a primary documented IC, (3) patients with an empirical secondarily documented IC (4) patients with candidemia; (5) patients who had another IC than candidemia (intra-abdominal candidiasis or deep-seated IC); (6) patients who had an IC due to susceptible species (excluding *C. glabrata* and *C.krusei*) (7) patients who had an IC due to *C. albicans*; (8) patients who had an IC due to non *albicans* species; (9) patients with a SOFA score higher than 6; (10) presence or absence of a septic shock (11) presence of a septic shock after excluding patients with IC due to *C. glabrata* and *C. krusei*. The secondary objective was to compare the effect of the initial SAT for adults ICU patients on the SOFA score at day 7. An IC was defined as primarily documented on the basis of either a positive direct examination, or the knowledge of the yeast identification on blood culture, per-operative sample or direct puncture of a sterile site, the day of SAT initiation. Conversely, the IC was defined as secondarily documented if the SAT was administered without documented evidence of infection.

**Statistical analysis**

A descriptive analysis of the patient's characteristics was performed using median and interquartile range for quantitative data and frequencies and percent for qualitative data. The

baseline characteristics of groups (ECH vs. AZO) were compared by the means of chi-square test for qualitative data, and Mann-Whitney test for quantitative data. To estimate the average causal effect of ECH on 28-day mortality, an inverse probability of treatment weight estimator (IPTW estimator) was used. The IPTW estimator is an extension of the propensity score[15]. The general principle of IPTW is to balance the distribution of baseline confounders across treatment groups, in order to reach the condition of a randomized controlled trial. Two modeling steps are required. The first step is to model the treatment assignment, i.e. the propensity to receive an echinocandin as initial SAT, which is needed to compute the weights by using a non parsimonious multivariate hierarchical logistic regression model, allowing accounting for center effect. The second step is to model the outcome as a function of the treatment in the weighted sample by using a Cox proportional hazard model. Some sensitivity analyses were performed for all sample by (1) excluding withdrawal patients (2) considering withdrawal patients as deceased (3) including patients with amphotericin B as initial SAT in the AZO group (4) excluding patients who received micafungin or anidulafungin from the ECH group. Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA.). A p-value of $<0.05$ was considered as significant.

## Results

### Patient characteristics

From 835 patients enrolled in the AmarCAND2 study, 397 patients who received either echinocandins (ECH: N=242; 61%) or azoles (AZO: N=155; 39%) as initial SAT were included in the present study (Figure 1). In the ECH group, patients had a higher median SAPS II score (48 [35; 62] vs. 43 [31; 58] p=0.01), a higher median Charlson index (6 [4 ; 7] vs. 4 [3 ; 6] p<.01) and were more frequently admitted for medical reasons (Table 1). Crude mortality was 34% in the ECH group and was significantly greater than in the AZO group (25%; p =0.04).

### SAT initiation and invasive candidiasis

At the time of SAT initiation, patients in the ECH group had a higher median SOFA score (8 [4; 11] vs. 6 [3; 8]), were more frequently in septic shock and more frequently exposed to central venous catheters, hemodialysis and vasoactive drugs. Primarily documented infection was observed in 185 patients in the ECH group (76.4%) and 100 cases in the AZO group (64.5%). The most frequent type of IC was candidemia in the ECH group and peritonitis in the AZO group. There was no difference in *Candida* species involved in the IC between both groups. The median time between the collection date of the positive sampling and SAT initiation was two days in both groups. However, when time was categorized, patients in ECH group had more frequently their SAT first administration one to two days after the collection date (p<0.01) (Table 1). Finally, the loading SAT dose followed guideline [1] for ECH: 70 mg for caspofungin (95%) and 100 mg for micafungin (100%). However, the loading dose for fluconazole was not adequate in the majority of patients: only 53 patients (35%) had a loading dose equal or above 12mg/kg, 38 patients (25%) had a loading dose ranked between 10 and 12 mg/kg and 61 patients (40%) had a loading dose lower than 10 mg/kg.

According to the available data from investigators, the majority of species were susceptible to the initial SAT administered (Table E1). Of note, there were 3 patients (1%) with IC due to *C. krusei*, including one resistant strain to fluconazole, and 20 patients (5%) with IC due to *C. glabrata*, including one resistant strain and 13 strains with intermediate susceptibility to fluconazole, treated by fluconazole as first SAT and 12 patients (3%) with IC due to *C. parapsilosis*, without resistant strain to caspofungin (Table E1).

Concerning the control of the source of infection, patients in the ECH group had more often the immediate removal of their intravascular devices (15.7%). The number of patients with more than two positive blood culture was 50 (20.7%) in ECH group and 14 (9%) in the AZO group.

Five days after SAT initiation, 73 patients (30%) were deescalated from echinocandin to fluconazole.

Finally, there was a higher proportion of AZO patients in a center with an infectious disease adviser within the ICU (94.2% in AZO group vs. 85.5% in ECH group).

Primary outcome

The following variables were retained in the weight model (Table E2): (1) Center variables: presence of a microbiology laboratory in the hospital, presence of a local protocol for antifungal therapy, and university hospital; (2) Variables at ICU admission: immunosuppression, comorbidity other than immunosuppression, and abdominal surgery; (3) Variables at SAT initiation: catheter removal, age, *Candida albicans* involved in IC, candidemia, central venous catheter, previous length of ICU stay, SOFA score, body temperature, blood cell transfusion, and administration of vasoactive drugs. After weighting and adjustment on baseline confounders, including the severity of illness, there was no significant association for echinocandins as initial SAT on 28-day mortality (HR: 0.95;

95%CI: [0.60; 1.49]; p=0.82) (Table 2). Sub-group analyses showed no significant association between echinocandins and outcome for all subgroups. Interestingly, removing the less susceptible species (*C. glabrata* and *C. krusei*) had no impact on the result (Figure 2). One sub-group analysis, focused on patients with septic shock, showed a trend to a beneficial effect of echinocandin as initial SAT, with a 54% decrease in 28-day mortality (HR: 0.46 [0.19; 1.07], p=0.07). Once again, the exclusion of patients with IC due to *C. glabrata* and *C. krusei*, which have a less susceptibility to echinocandins or azoles had no impact on the result (HR: 0.43 [0.16; 1.13], p=0.09). Finally, sensitivity analyses showed no difference in the result.

To attempt to capture IC attributable mortality, we postulated that early deaths (7-day mortality) are more related to the IC than the late ones. There were 50 patients who died within 7 days after SAT initiation, 20 in the AZO group (12.90%) and 30 in the ECH group (12.4%) (p=0.88). In a sensitivity analysis, the risk of death was not different in both groups (HR: 0.36 [0.07; 1.86], p=0.23 – Data not shown).

Secondary outcome

At day 7, there was no significant difference in the variation of SOFA score for both groups. Delta sofa at day 7 was 2 (IQR: [-1 ; 4]) in AZO group and 2 (IQR: [0 ; 4]) in ECH group, p=0.68.

**Discussion**

This study based on a large prospective multicenter ICU cohort showed that echinocandin was the main SAT administered in the case of primarily documented IC and in case of candidemia. The comparison between echinocandins or azoles as initial SAT failed to show a beneficial effect of echinocandin on prognosis in non-neutropenic ICU patients. Only patients with septic shock had a marginal improvement of prognosis with an echinocandin as initial SAT.

Echinocandin is the most recently developed family of antifungal agents, characterized by a broader spectrum of antifungal activity with few adverse events. Due to their characteristics, they replaced fluconazole as first line antifungal therapy in case of documented invasive candidiasis for non-neutropenic ICU patients [2, 16]. The last update of IDSA guideline for invasive candidiasis confirmed the echinocandins as first line antifungal therapy [1], although few data are available to confirm the beneficial of this strategy compared to fluconazole.

There were a low number of trials focusing on the comparison of echinocandin and fluconazole in the treatment of invasive candidiasis [17]. In their meta-analysis, Wang *et al*. concluded that echinocandins were as effective as azoles either for prophylaxis or treatment of patients with fungal infections [17]. Moreover, a meta-analysis focusing on *C. parapsilosis* infection showed that, although echinocandins are as effective as fluconazole, there was no benefit of echinocandins on patient prognosis [18].

In, a recent retrospective multicenter study included patients with intra-adbominal candidiasis, Lagunes et al. also showed that echinocandin (as compared to fluconazole) was more frequently administered as initial SAT in patients with a higher severity score, septic shock or candidaemia. After adjustment on confounders using a multivariate logistic regression, the initial empirical therapy did not influence the outcome [19].

In the case of empirical therapy, there was no evidence for echinocandin superiority and ESCMID guidelines had no suggestion about the nature of the initial SAT [2]. Conversely, the new IDSA guidelines recommend echinocandins as preferred empiric therapy in non-neutropenic patients in ICU [1]. This new recommendation is a change compared to the last one where echinocandins were recommended when patients were previously treated by azoles, but was not based on new evidence [16]. In the recent EMPIRICUS trial, comparing empirical micafungin and placebo in mechanically ventilated patients with sepsis, there was no evidence for a benefit in survival [20]. Here, we did not show any beneficial effect of echinocandins in case of secondarily proven IC. A possible explanation was the fact that patients on echinocandin group seem to have been treated later than patients in the azole group (Table 1), while it is well know that time to treatment initiation is a main independent factor for survival in ICU [21, 22]. In addition, the pharmacokinetics of antifungal agents might be altered in critically ill patients [23].

In the case of targeted therapy, ESCMID and IDSA guidelines recommend echinocandin as first line drug [1, 2]. This recommendation was based on the result of the trial of Reboli *et al.*, which compared anidulafungin and fluconazole. But the conclusion of the trial is only that anidulafungin was non-inferior to fluconazole, and there was no evidence that anidulafungin was significantly associated to an improvement of the patient prognosis [11]. Our results showed no significant difference between azoles and echinocandins in case of primarily diagnosed IC.

Delaying intra-vascular device removal is a risk factor for mortality [21], and last IDSA guideline confirmed the necessity to remove central venous catheter as early as possible [1]. Here, patients with echinocandins as first SAT were more exposed to the immediate removal of central venous catheter than patients with fluconazole as initial SAT. It was introduced as a confounder in the multivariable analysis. After adjustment for measured confounders,

echinocandins stay as effective as fluconazole for IC, and there was no difference which was observed on patient prognosis.

Moreover, we failed to show that echinocandin as initial treatment improves the prognosis of patients either in case of candidemia or of intra-abdominal candidiasis. By considering separately *Candida albicans* or other *Candida* species, there was no significant difference between both antifungal families.

Finally, we explored the variation of the SOFA score between SAT initiation and day 7 after SAT initiation, and there was no significant difference between both antifungal classes. This result is likely explained by the overall susceptibility of the *Candida* strains to the initial SAT, according to the available data.

This study has several strengths. It is probably the largest prospective cohort of patients treated by azoles or echinocandins in ICU exclusively for primarily or secondarily invasive candidiasis. The data collection allowed using adapted methods of the counterfactual theory to adjust for measured confounders [15]. Finally, measure of MIC showed that there was few resistant strains observed, and sensitivity analyses excluding the less susceptible *Candida* species showed no modification in the result.

However, this study had several limitations. First, it was an observational study without randomization for treatment. Indeed, some unmeasured confounders could influence the results, in particular the reasoning of the decision to treat by echinocandin or fluconazole. Second, there were no time-dependent variables included in the model, which would have allowed accounting for the evolution of the patient's state of health during time. Indeed, the evolution of the patient health during the stay implies a modification of the risk of IC onset, day after day, which also leads to a modification of the patient prognosis. Not accounting for a time-dependent confounder was a potential bias to the assessment of the impact of SAT on

prognosis. Third, the loading dose of fluconazole was lower than 12 mg/kg in two-third of the cases. But even in this subgroup with a loading dose lower than recommended, echinocandin use did not improve the prognosis. Fourth, only non-neutropenic ICU patients were included. So these results cannot be directly extrapolated to other patients, such as oncology patients. Finally, biomarkers were not frequently used in participating ICUs, so it was difficult to assess the impact of biomarkers or scoring systems for the choice of preemptive antifungal therapy. Further studies should be performed to assess the impact of echinocandins compared to azole in specific settings such as oncology patients, or in ICUs that utilize biomarkers or scoring systems for earlier initiation of preemptive therapy for IC.

To conclude, in a large multicentre cohort of non-neutropenic ICU patients, we failed to show a beneficial effect of echinocandins as initial SAT on patient prognosis, comparatively to azoles. The results suggested only that echinocandins should be preferred for ICU patients with septic shock. This should be confirmed by a randomized clinical trial or a larger cohort study involving ICU patients with a septic shock and including time-dependent confounders. If the choice of echinocandin as first line SAT should be based on the wider antifungal spectrum, a strong safety profile and the theoretical advantage of a lower potential for resistance selection, according to the last IDSA guideline [1], the trend toward a better outcome cannot be confirmed, based on our results. The choice between echinocandin and azole should be based on the azole-resistance profile and the improved safety, more than on the trend toward a better outcome. This is especially important given the fact that the previous antifungal use impacts on the further emergence of antifungal resistance. Finally, a more appropriate choice of early antifungal therapy is reliant on the development of more precocious culture-independent diagnostic tools, such as the T2 nanotechnology or B-D-glucan assay. Further prospective studies including these new methods may lead to more precise recommendations to select the best initial antifungal therapy.

**Conflicts of interest:**

EA has been a consultant to Astellas, Alexion, Cubist, Gilead and MSD, and has benefited from grants to his research unit from Gilead and Pfizer. CB is an employee of MSD France. J-MC has been a consultant to MSD. HD has been a consultant to Astellas, Gilead, Cubist, Astra-Zeneca, Merck and Pfizer. J-PG has been a consultant to Astellas, Gilead, Merck and Pfizer. DG has benefited from grants of the Principalty of Monaco to his research unit. OLeroy has been consultant to Astellas, Gilead, Merck, Novartis, Pfizer and Sanofi. OLortholary has been consultant to Gilead Sciences and Novartis and member of the speaker's bureau of Astellas, Basilea, Merck, and Pfizer. J-PM has been a consultant to Astellas, Gilead, MSD, and LFB. PM has been a consultant to Astra-Zeneca, Astellas, Basilea, MSD, Pfizer, Tetraphase and TMC. P-FP has been a consultant to MSD and Pfizer. JFT has given lectures for symposiums set up by Astellas, Pfizer, MSD, 3M, Novartis, and Gilead; has benefited from unrestricted research grants to his research unit from 3M, MSD, and Astellas; and has been a consultant involved in scientific boards for MSD, 3M, and Bayer. SB has no conflict of interest.

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Table 1: Patients' characteristics according to their group of initial systemic antifungal therapy (N=397 patients)

| Characteristics | SAT group Azoles N=155 | SAT group Echinocandins N=242 | p-value |
|---|---|---|---|
| Center characteristics | | | |
| Number of hospitalization bed (>1040) | 71 (45.8) | 124 (51.2) | 0.29 |
| University hospital | 112 (72.3) | 179 (74) | 0.71 |
| Infectious disease unit within the hospital | 124 (80) | 205 (84.7) | 0.22 |
| Microbiology laboratory within the hospital | 132 (85.2) | 229 (94.6) | <.01 |
| Infectious disease adviser at the ICU | 146 (94.2) | 207 (85.5) | <.01 |
| Protocol for SAT prescription | 72 (46.5) | 148 (61.2) | <.01 |
| Protocol for SAT de-escalation | 127 (81.9) | 220 (90.9) | <.01 |
| Baseline characteristics of the patients | | | |
| Age | 63.8 [53.1 ; 73.8] | 61.9 [53 ; 73.8] | 0.54 |
| Sex (Male) | 98 (63.2) | 153 (63.2) | 0.99 |
| BMI | 24.6 [21.7 ; 29.4] | 26.7 [22.9 ; 31.3] | 0.02 |
| Previous duration of hosp stay (days) | 1 [0 ; 8] | 2 [0 ; 10] | 0.52 |
| Previous duration of ICU stay (days) | 4 [1 ; 11] | 5 [1 ; 13] | 0.11 |
| SAPSII at ICU admission | 43 [31 ; 58] | 48 [35 ; 62] | 0.01 |
| SOFA score at ICU admission | 8 [5 ; 10] | 9 [6 ; 12] | <.01 |
| Charlson index | 4 [3 ; 6] | 6 [4 ; 7] | <.01 |
| Immunosuppression | | | |
| Corticosteroid therapy | 5 (3.2) | 10 (4.1) | 0.64 |
| AIDS | 3 (1.9) | 3 (1.2) | 0.58 |
| Other | 13 (8.4) | 23 (9.5) | 0.71 |
| Surgery just before[§] or during ICU stay | 122 (78.7) | 160 (66.1) | <.01 |
| Type of ICU admission | | | 0.01 |
| Medicine | 45 (29) | 105 (43.4) | |
| Elective surgery | 13 (8.4) | 25 (10.3) | |
| Emergency surgery | 87 (56.1) | 104 (43) | |
| Other (trauma, burn) | 10 (6.5) | 8 (3.3) | |
| At SAT initiation in the ICU | | | |
| Body temperature (>38°C) | 37.6 [37 ; 38.3] | 38 [37 ; 38.6] | 0.05 |
| SOFA score | 6 [3 ; 8] | 8 [4 ; 11] | <.01 |
| Septic shock | 55 (35.5) | 124 (51.2) | <.01 |
| Severe sepsis | 67 (43.2) | 98 (40.5) | 0.59 |
| Invasive mechanical ventilation | 106 (68.4) | 179 (74) | 0.23 |
| Central venous catheter | 145 (93.5) | 237 (97.9) | 0.03 |
| Urinary catheterization | 149 (96.1) | 234 (96.7) | 0.77 |
| Hemodialysis or hemodiafiltration | 33 (21.3) | 86 (35.5) | <.01 |
| Total parenteral nutrition | 78 (50.3) | 119 (49.2) | 0.82 |

| | | | |
|---|---|---|---|
| Vasoactive drug administered | 67 (43.2) | 140 (57.9) | <.01 |
| Antibacterial treatment | 145 (93.5) | 214 (88.4) | 0.09 |
| Corticosteroid treatment | 26 (16.8) | 54 (22.3) | 0.18 |
| Red blood cell transfusion in ICU | 78 (50.3) | 139 (57.4) | 0.16 |
| Platelet transfusion in ICU | 25 (16.1) | 58 (24.0) | 0.06 |
| Creatinine (µmol/L) | 95 [53 ; 161] | 119 [74 ; 205] | <.01 |
| Control of the source or follow-up of the infection | | | |
| Immediate removal of intravascular devices[†] | 12 (7.7) | 37 (15.3) | 0.03 |
| More than two positive blood cultures | 14 (9) | 50 (20.7) | <.01 |
| Invasive candidiasis | | | |
| Primary documented invasive candidiasis | 100 (64.5) | 185 (76.4) | <.01 |
| Type of *Candida* infection | | | <.01 |
| Candidemia | 35 (22.6) | 118 (48.8) | |
| Peritonitis | 92 (59.4) | 92 (38.0) | |
| Deep-seated candidiasis | 28 (18.1) | 32 (13.2) | |
| *Candida* species | | | |
| *Candida albicans* | 108 (69.7) | 149 (61.6) | 0.1 |
| *Candida* non *albicans* | | | |
| *Candida glabrata* | 21 (13.5) | 43 (17.8) | 0.26 |
| *Candida parapsilosis* | 4 (2.6) | 14 (5.8) | 0.13 |
| *Candida krusei* | 3 (1.9) | 8 (3.3) | 0.42 |
| *Candida tropicalis* | 4 (2.6) | 11 (4.5) | 0.32 |
| Time between positive sampling and initial SAT | | | |
| Median (days)[IQR] | 2 [1 ; 3] | 2 [1 ; 2] | 0.62 |
| 0 days | 50 (32.3) | 63 (26) | <0.01 |
| 1-2 days | 54 (34.8) | 124 (51.2) | |
| >2 days | 51 (32.9) | 55 (22.7) | |

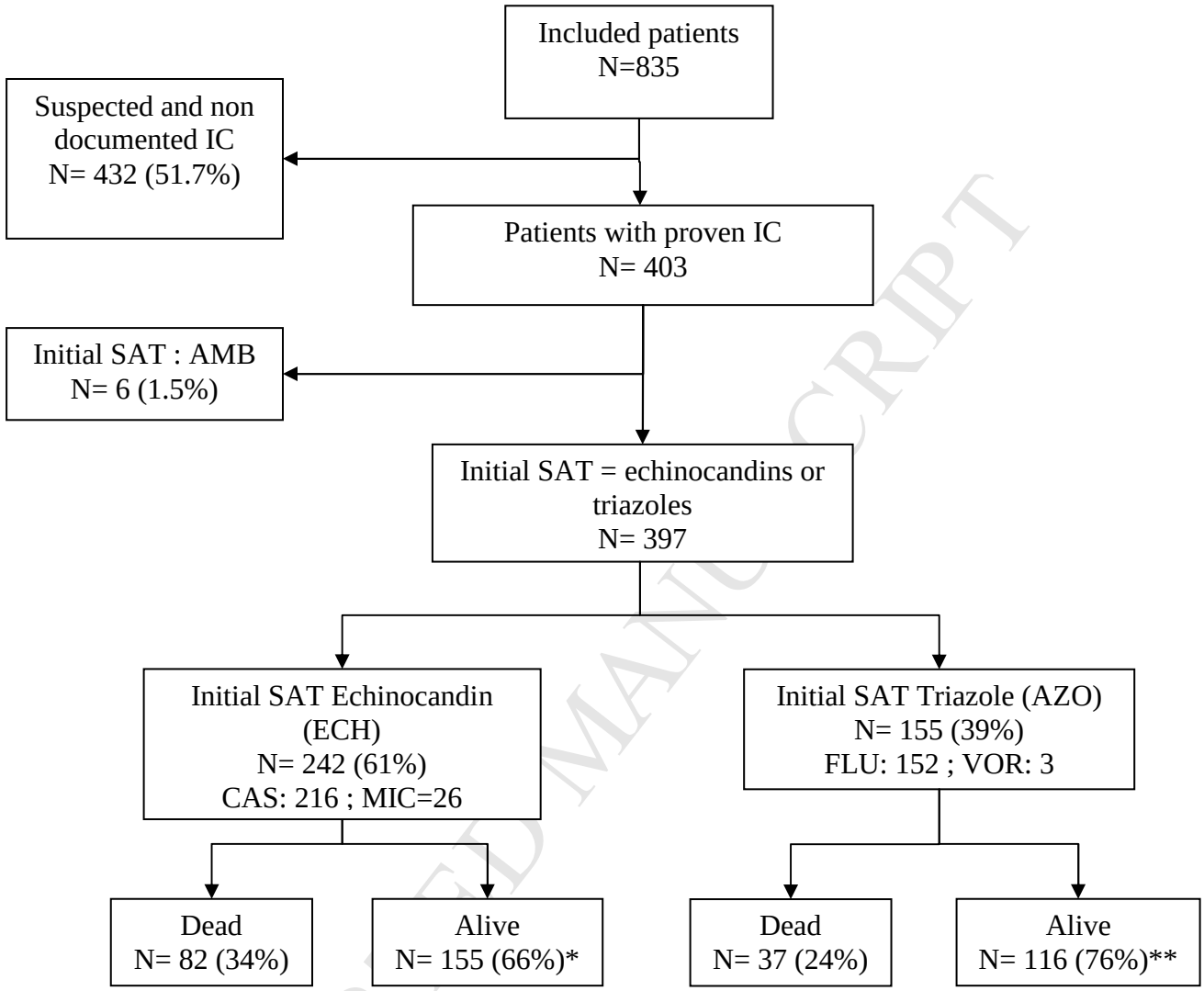
[ε]: surgery with ten days prior to ICU admission; [†] Immediate removal of intravascular devices: removal of the central catheter or the arterial catheter or the dialysis catheter on SAT day.

SAT: systemic antifungal treatment; ICU: intensive care unit; BMI: body mass index; IQR: interquartile range

Table 2: Multivariate stratified Cox analysis for the primary objective using Inverse Probability Treatment Weight estimator (N=397 patients)

| | HR [95%CI] | p-value |
|---|---|---|
| Initial SAT = Echinocandins | 0.95 [0.60 ; 1.49] | 0.82 |
| *Candida albicans* | 1.20 [0.81 ; 1.77] | 0.36 |
| Abdominal surgery | 0.60 [0.38 ; 0.94] | 0.02 |
| Candidemia | 1.14 [0.66 ; 1.96] | 0.63 |
| Septic shock | 1.50 [0.99 ; 2.26] | 0.05 |
| Catheter removal on SAT initiation day | 0.90 [0.47 ; 1.71] | 0.74 |
| Primarily documented IC | 1.73 [1.04 ; 2.89] | 0.03 |
| SAPSII at ICU admission | | <0.01 |
| <41 | 0.24 [0.13 ; 0.43] | |
| 41 – 64 | 0.58 [0.36 ; 0.94] | |
| >64 | = Ref | |

Figure 1: Flow chart

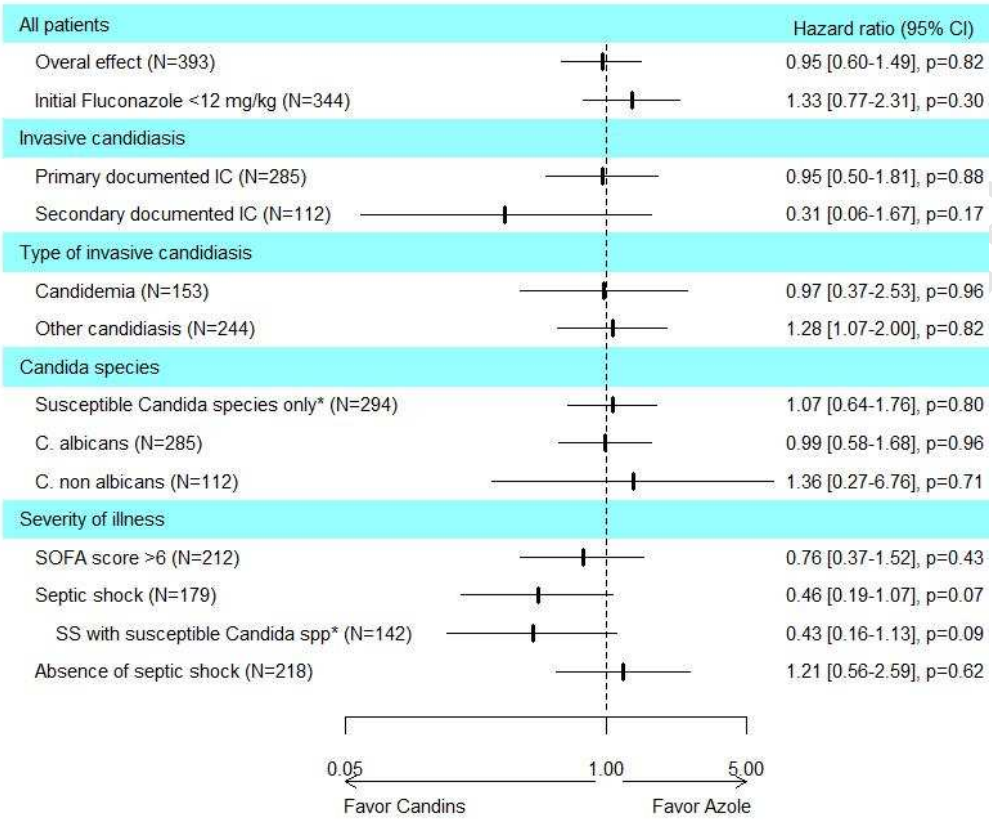



ECH: Echinocandins, AZO: azoles; FLU: Fluconazole, VOR: Voriconazole, CAS: Caspofungin, MIC: micafungin SAT: Systemic Antifungal Treatment AMB: Amphotericin B

*Echinocandins: withdrawal =6 (2.5%)

**Azoles: withdrawal = 2 (1.3%)

Figure 2: Summary of the results for the primary outcome: impact of echinocandins as initial SAT on the 28-day prognosis (N=397).




If HR>1 azole as initial SAT is protective for 28-day mortality. If HR<1: echinocandin as initial SAT is protective for 28-day mortality.

*SS: Septic shock with susceptible *Candida* spp: Patients with IC due to *C. glabrata* or *C. krusei* were excluded from the analysis. N=142.