Intensive Care Med (2015) 41:1931–1940
DOI 10.1007/s00134-015-4053-1

ORIGINAL

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# Antifungal de-escalation was not associated with adverse outcome in critically ill patients treated for invasive candidiasis: post hoc analyses of the AmarCAND2 study data

Received: 1 July 2015
Accepted: 1 September 2015
Published online: 14 September 2015


**Take-home message:** Early de-escalation of systemic antifungal treatments is not consensual. A causal analysis based on a multicenter prospective cohort in 87 French ICUs has shown that antifungal de-escalation within a 5-day interval is safe in SAT-treated non-neutropenic adult intensive care unit patients.

**Electronic supplementary material**
The online version of this article (doi:10.1007/s00134-015-4053-1) contains supplementary material, which is available to authorized users.

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**Abstract** *Purpose:* Systemic antifungal therapy (SAT) of invasive candidiasis needs to be initiated immediately upon clinical suspicion. Controversies exist about adequate time and potential harm of antifungal de-escalation (DE) in documented and suspected candidiasis in ICU patients. Our objective was to investigate whether de-escalation within 5 days of antifungal initiation is associated with an increase of the 28-day mortality in SAT-treated non-neutropenic adult ICU patients. *Methods:* From the 835 non-neutropenic adults recruited in the multicenter prospective observational AmarCAND2 study, we selected the patients receiving systemic antifungal therapy for a documented or suspected invasive candidiasis in the ICU and who were still alive 5 days after SAT initiation. They were included into two groups according to the occurrence of observed SAT de-

escalation before day 6. The average causal SAT de-escalation effect on 28-day mortality was evaluated by using a double robust estimation. *Results:* Among the 647 included patients, early de-escalation at day 5 after antifungal initiation occurred in 142 patients (22 %), including 48 (34 %) patients whose SAT was stopped before day 6. After adjustment for the baseline confounders, early SAT de-escalation was the solely factor not associated with increased 28-day mortality (RR 1.12, 95 % CI 0.76–1.66). *Conclusion:* In non-neutropenic critically ill adult patients with documented or suspected invasive candidiasis, SAT de-escalation within 5 days was not related to increased day-28 mortality but it was associated with decreased SAT consumption. These results suggest for the first time that SAT de-escalation may be safe in these patients.

**Keywords** Antifungal · Intensive care unit · De-escalation · Invasive candidiasis · Causal inference · Sepsis · Outcome

## Introduction

*Candida* species are one of the most frequently recovered pathogens in patients with hospital-acquired bloodstream infections and the most common cause of invasive fungal infection [1–3], which is associated with a mortality rate from 30 % to more than 60 % in the case of septic shock [4–8].

Early treatment of invasive candidiasis (IC) improves patients' prognosis [4, 6, 8, 9]. Given the poor sensitivity of blood culture to diagnose IC [10], guidelines recommend to initiate systemic antifungal therapy (SAT), mostly an echinocandin, for critically ill patients with risk factors for IC and no other known cause of fever. This approach is considered valid by many experts while waiting for further evidence. The general opinion is that the administration of SAT should be guided by the evaluation of risk factors, the use of clinical prediction rules, culture data from non-sterile sites, and biological markers [11].

Unfortunately, no diagnostic tests are available to firmly confirm or discard the diagnosis of IC in the absence of positive blood cultures or non-contaminated positive sample from a sterile site. Therefore the management of antifungal treatment in suspected non-proven invasive fungal infection is speculative.

A cross-sectional multicenter study showed that SAT was administered to 7.5 % of ICU patient-days, although two-thirds of them had no documented invasive fungal infection [12]. Possible consequences of these practices are an increase of cost and selection of more resistant yeasts [13, 14].

Similarly, the positive predictive value for IC of the prediction rules in a general ICU population was lower than 20 % in the most recent studies [15–17] and systematic pre-emptive strategies in such predetermined patients failed to improve patients' prognosis [15, 18].

Echinocandins are the first-line therapeutic option for IC, because of fungicidal activity, good tolerance, and a broad-spectrum activity [19, 20]. For IC, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and Infectious Diseases Society of America (IDSA) guidelines recommend a de-escalation strategy (3 days in stabilized patients, as per IDSA, and 10 days overall, as per ESCMID) to limit the emergence of resistant strains and to reduce treatment costs [19, 20]. However, the level of recommendation is poor because of the lack of available data. The safety of de-escalation in the case of proven candidiasis has been recently suggested by prospective non-comparative studies [21, 22], but no comparative study exists for proven or probable IC treated in the ICU.

The objective of this study is to investigate whether de-escalation or stopping of SAT within 5 days of initiation is associated with an increase in 28-day mortality in SAT-treated non-neutropenic adult ICU patients. We used a marginal structural model (MSM) to assess the causal relationship of de-escalation on day-28 prognosis using the prospective multicenter observational French study AmarCAND2.

## Materials and methods

### Study design

The patients were selected from AmarCAND2, a multicenter, prospective, observational study conducted in French ICUs during 1 year (2012–2013). The investigating centers were ICUs having managed at least one IC case within the past year and willing to participate in 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 count at most 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 collection and definition

Data were collected for each patient using an electronic case report at study inclusion and throughout the study. The following data were collected: demographics data, severity scores (at inclusion, at SAT administration, at day 7 after SAT administration), clinical data at SAT administration, mycological data for confirmed invasive *Candida* infection, and information on the treatment. If the initial treatment was modified, the investigator was asked to record the date and reason(s) for the modification and information about the modification. At the end of the SAT, the following data were recorded: the SAT end date and the outcome of the *Candida* infection. The dates of ICU and hospital discharges were also collected, as was the vital status of all patients 28 days after the SAT initiation (alive, dead, or lost to follow-up after ICU discharge).

### Studied population

AmarCAND2 patients who were still alive in the ICU at day 5 after the first SAT administration were included in the present study. Patients were divided into two groups according to the SAT strategy observed within 5 days following SAT initiation: (1) de-escalation group (DE) and (2) absence of de-escalation group (NoDE). SAT de-escalation was defined as either a switch from initial SAT drugs (except fluconazole) to fluconazole or termination of initial SAT drugs within 5 days following SAT initiation.

### Study outcomes

The primary outcome was to evaluate whether SAT de-escalation within 5 days of SAT initiation was, or not, associated with the worsening of the 28-day mortality as compared to the mortality of adult non-neutropenic ICU patients who received SAT without any de-escalation. Subgroup analyses of the primary objective were performed for (1) patients with SAT de-escalation observed within 7 days after SAT initiation (allowing variation of SOFA score between SAT day and day 7 to be added in the model as an adjustment covariate); (2) patients who had a documented IC at day 5 (including a distinction between patients with *C. albicans* IC or patients with *C.* non-*albicans* IC); (3) patients who did not have a documented IC at day 5; (4) Patients with echinocandins as initial SAT; (5) patients with fluconazole as initial SAT; (6) patients without secondary location for *Candida*; (7) ICUs belonging to large hospitals with more than 1040 hospitalization-beds. Secondary objectives were to evaluate (1) if stopping SAT before day 5 is, or not, associated with the worsening of the 28-day mortality as compared to the mortality of adult non-neutropenic ICU patients without proven invasive candidiasis at day 5 and whose SAT was not stopped; (2) to compare the effect of SAT de-escalation for adults ICU patients on (a) SOFA score at day 7; (b) the length of ICU stay; (c) the number of days alive after ICU discharge; (d) the duration of SAT administration; (e) the number of days alive after the end of SAT.

### 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 (DE vs. NoDE) were compared by means of the Chi-squared test for qualitative data and Mann–Whitney test for quantitative data. To estimate the average causal effect of DE on 28-day mortality, a double robust (DR) inverse probability of treatment weight (IPTW) estimator was used. The DR-IPTW estimator is an extension of the IPTW estimator [23]. 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 [24]. Two modeling steps are required. The first step is to model the treatment assignment, i.e., the propensity which is needed to compute the weights. The second step is to model the outcome as a function of the treatment in the weighted sample. When the treatment and the outcome are both binary, each modeling step usually relies on logistic regression models. Such regression models rely on strong assumptions about the underlying data distribution and may therefore be misspecified. DR-IPTW estimators were developed to prevent the consequence of model misspecification. This adaptation of the IPTW estimators guaranties consistency if only one of the two models is correctly specified and efficiency if they are both correctly specified [25]. The DR-IPTW estimator has a marginal interpretation, which corresponds to the average treatment effect, i.e., the difference in outcome had all patients being exposed to SAT de-escalation versus all patients being free from SAT de-escalation after adjustment for all measured confounders. The final results were expressed as relative risk (RR) for 28-day mortality between the two exposed pseudo-populations with bootstrapped standard errors and 95 % confidence intervals. Post hoc power analyses were performed for primary and secondary objectives. The

robustness of the results was confirmed by IPTW models. Statistical analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC, USA). The SAS Macro developed by Funk et al. was used for the DR estimation [26]. A $p$ value less than 0.05 was considered significant. Details on the power calculation are given in the Electronic Supplementary Material (ESM).

## Results

### Patient characteristics

From 835 patients enrolled in the AmarCAND2 study, 647 (77.5 %) who were still alive in the ICU 5 days after SAT initiation were included in the present study. Of the 647 included patients, 142 (22 %) experienced a SAT de-escalation or a SAT stop within 5 days of SAT initiation and 505 (78 %) were in the NoDE group (Fig. 1). Patients in the DE group were younger and had a shorter previous ICU stay but their SAPS II or SOFA scores at ICU admission were similar (Table 1). The rate of proven IC was not different between DE and NoDE groups (Table 2). Seven days after SAT initiation, SOFA score was not different between DE and NoDE groups (Table 3).

### Initial SAT and SAT de-escalation

The use of echinocandins as first SAT was more frequent in the DE group (89 %) (Table 2). In the DE group, the median delay before SAT modification was 3 days (IQR 2; 4). A total of 94 patients (66 %) experienced a SAT de-escalation to fluconazole at a median dose of 800 mg (IQR 400; 800) and 48 patients (34 %) experienced a SAT stop within 5 days of initial SAT. Removal of a central catheter on the SAT initiation day was observed for 15 patients (58 %) in the DE group and for 23 patients (29 %) in the NoDE group ($p < 0.01$) (more details on removal of the possible source of infection are given Table E1 in ESM). The median duration of SAT was 11 days (IQR 7; 16) in the 323 remaining patients for whom the reason for SAT discontinuation was not recorded. Finally, antifungal prescriptions were defined into written procedures in 47 (61 %) ICUs and the de-escalation procedure was declared to follow international guidelines in 58 (75 %) ICUs. The existence of both types of procedures was not associated with the decision to de-escalate (Table 1).

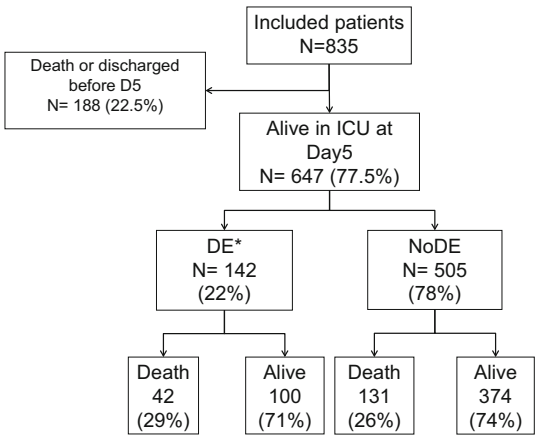


**Fig. 1** Overall flow chart (primary objective). *SAT stop: $N = 48$. *ICU* intensive care unit, *SAT* systemic antifungal therapy, *D5* day 5 after SAT initiation, *DE* SAT de-escalation group at day 5 included patients with a SAT de-escalation or a SAT stopping observed between D0 and D5 after SAT initiation, *NoDE* absence of SAT de-escalation at day 5, *Death* 28-day mortality

### Characteristics of patients with an invasive candidiasis at day 5

There was no difference between both groups regarding the characteristics of the patients and the evolution of the invasive candidiasis for the patients with an IC at day 5. In particular, the rates of clinical failure, or of death, were not different between DE and NoDE groups in both documented and non-documented IC (more details on the characteristics of the patients with an IC are given in Tables E2 and E3 in ESM).

### Primary outcome

On the basis of the double robust estimation, the de-escalation strategy within 5 days had no significant impact on the 28-day mortality compared to non de-escalation strategy (relative risk 1.12, 95 % CI 0.76–1.66). Details on variables used for the double robust estimation are provided in Tables E4 and E5 in ESM. The sensitivity analysis of patients with a SAT de-escalation before day 7 gave similar results (RR 0.95 [0.66; 1.36]). Results remained unchanged in prespecified subgroups, more particularly for documented IC, non-documented IC, and first-line treatment with candins (Fig. 2). Moreover, subgroup analysis excluding suspected IC with *C. glabrata* or *C. krusei* showed no difference. The results using an IPTW estimator confirmed the double robust estimation model that we used (Table E6 in ESM).

### Secondary outcomes

Early SAT de-escalation was associated with a decrease in the length of ICU stay (14 days [9; 28] vs. 19 days [11;

**Table 1** Patient characteristics according to the de-escalation status at day 5 of systemic antifungal therapy ($N = 647$)

| Characteristics | Systemic antifungal therapy group | | $p$ value |
|---|---|---|---|
| | De-escalation ($N = 142$) | No de-escalation ($N = 505$) | |
| Center characteristics* | | | |
| University hospital | 33 (84.6) | 125 (69.8) | 0.78 |
| Type of ICU | | | 0.19 |
| Medical | 17 (12.0) | 79 (15.6) | |
| Surgery | 28 (19.7) | 136 (26.9) | |
| Polyvalent | 97 (68.3) | 290 (26.9) | |
| Protocol for SAT prescription | 86 (60.6) | 275 (54.4) | 0.57 |
| Protocol for SAT de-escalation | 39 (27.4) | 179 (35.5) | 0.14 |
| Baseline characteristics | | | |
| Age | 61.2 [51.5; 71.7] | 63.7 [54.8; 73] | 0.04 |
| Sex (Male) | 90 (63.4) | 322 (63.8) | 0.93 |
| Body mass index | 27.5 [22.9; 32.9] | 25.9 [22.6; 30.4] | 0.06 |
| Previous duration of hospital stay (days) | 2 [0; 9] | 2 [0; 9] | 0.91 |
| Previous duration of ICU stay (days) | 4 [0; 11] | 5 [1; 13] | 0.04 |
| SAPS II score | 48.5 [38; 58] | 47 [36; 59] | 0.52 |
| SOFA score at ICU admission | 8 [6; 11] | 8 [5; 11] | 0.35 |
| Presence of comorbidities[a] | 4 [2; 6] | 4 [3; 6] | 0.50 |
| Immunosuppression | 103 (72.5) | 360 (71.3) | 0.77 |
| Corticosteroid therapy | 4 (2.8) | 23 (4.6) | 0.36 |
| AIDS | 4 (2.8) | 7 (1.4) | 0.44 |
| Other | 14 (9.9) | 53 (10.5) | 0.83 |
| Surgery just before or during ICU stay | 95 (66.9) | 330 (65.3) | 0.73 |
| Type of ICU admission | | | 0.16 |
| Medicine | 61 (43) | 234 (46.3) | |
| Elective surgery | 8 (5.6) | 44 (8.7) | |
| Emergency surgery | 69 (48.6) | 200 (39.6) | |
| Other (trauma, burn) | 4 (2.8) | 27 (5.3) | |
| At the initiation of the SAT in the ICU | | | |
| Body temperature | 38 [37; 38.8] | 38 [37; 38.5] | 0.53 |
| SOFA score | 8 [5; 11] | 8 [5; 10] | 0.38 |
| Septic shock | 86 (60.6) | 272 (53.9) | 0.16 |
| Severe sepsis | 53 (37.3) | 198 (39.2) | 0.68 |
| Invasive mechanical ventilation | 117 (82.4) | 417 (82.6) | 0.96 |
| Central venous catheter | 141 (99.3) | 488 (96.6) | 0.09 |
| Urinary catheterization | 133 (93.7) | 481 (95.2) | 0.45 |
| Hemodialysis or hemodiafiltration | 39 (27.5) | 165 (32.7) | 0.24 |
| Total parenteral nutrition | 48 (33.8) | 244 (48.3) | <0.01 |
| Vasoactive drug | 90 (63.4) | 311 (61.6) | 0.70 |
| Antibacterial treatment | 117 (82.4) | 461 (91.3) | <0.01 |
| Corticosteroid treatment | 33 (23.2) | 126 (25) | 0.68 |
| Red blood cell transfusion in ICU | 67 (47.2) | 297 (58.8) | 0.01 |
| Platelet transfusion in ICU | 18 (12.7) | 114 (22.6) | <0.01 |
| Creatinine (μmol/L) | 125 [70; 197] | 105 [63; 178] | 0.10 |

The results are given as $n$ (%) or median ± interquartile range [Q1; Q3]

$p$ value: Chi-square test for qualitative variables, Mann–Whitney test for quantitative variables

*ICU* intensive care unit, *SAT* systemic antifungal therapy, *SAPS* simplified acute physiology score, *SOFA* sequential organ failure assessment, *AIDS* acquired immunodeficiency syndrome

* $p$ value for center characteristics was obtained using an univariate hierarchical model

[a] Comorbidities: myocardial infarction, congestive heart failure, peripheral venous disease, hemopathy, solid organ transplant, stroke, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, diabetes (with or without organ damage), mild or severe chronic kidney disease, hemiplegia, solid tumor, mild or severe chronic liver disease

35] group $p < 0.01$), and a decrease in the SAT duration. The number of days alive without SAT at day 28 was higher in the DE group (14 days [5; 23]) than in the NoDE group (10 days [2; 17] $p < 0.01$). On the basis of the cost of echinocandin agents in France, we calculated median costs in each DE group. It was 2835 € in the NoDE group (IQR 171; 7371) and 1743 € in the DE group (IQR 1134; 2382). The improvement of the SOFA score at day 7 was similar in both groups (Table 3). Clinical and microbiological failure rates were strictly

**Table 2** Type of initial systemic antifungal therapy and invasive candidiasis according to patient group ($N = 647$)

| Characteristics | systemic antifungal therapy group | | *p* value |
|---|---|---|---|
| | De-escalation ($N = 142$) | No de-escalation ($N = 505$) | |
| Type of initial systemic antifungal therapy | | | <0.01 |
| Amphotericin B | 0 (0) | 10 (2) | |
| Fluconazole | 15 (10.6) | 246 (48.7) | |
| Voriconazole | 0 (0) | 4 (0.8) | |
| Echinocandins | 127 (89.4) | 245 (48.5) | |
| At day 5 after SAT initiation | | | |
| Documented invasive candidiasis | 70 (49.3) | 206 (40.8) | 0.07 |
| Type of *Candida* infection | | | |
| Candidemia | 32 (22.5) | 82 (16.2) | 0.08 |
| Other invasive candidiasis | 41 (28.9) | 140 (27.7) | 0.58 |
| Deep-seated candidiasis | 12 (8.5) | 38 (7.5) | 0.72 |
| Complicated intra-abdominal infection | 29 (20.4) | 102 (20.2) | 0.95 |
| *Candida* species[a] | | | |
| *Candida albicans* | 62 (43.7) | 131 (25.9) | <0.01 |
| *Candida* non-*albicans* | 12 (8.5) | 91 (18.0) | <0.01 |
| *Candida glabrata* | 6 (4.2) | 47 (9.3) | 0.05 |
| *Candida parapsilosis* | 1 (0.7) | 15 (3.0) | 0.12 |
| *Candida krusei* | 0 (0) | 9 (1.8) | 0.11 |
| *Candida tropicalis* | 3 (2.1) | 10 (2.0) | 0.92 |

*SAT* systemic antifungal therapy
[a] Data only available for documented invasive candidiasis

**Table 3** Results for the secondary outcome

| Characteristics | Systemic antifungal therapy (SAT) group | | *p* value |
|---|---|---|---|
| | De-escalation ($N = 142$) | No de-escalation ($N = 505$) | |
| SOFA score at day 7 after initial SAT | 5 [3; 9] | 5 [2; 9] | 0.90 |
| Delta SOFA score from SAT to day 7 | 2 [−1; 4] | 2 [0; 4] | 0.46 |
| Length of ICU stay after initial SAT (days) | 14 [9; 27] | 19 [11; 35] | <0.01 |
| Length of SAT administration (days) | 12 [5; 16] | 14 [8; 21] | <0.01 |
| Number of days alive without SAT at day 28 | 13 [5; 23] | 10 [1; 17] | <0.01 |
| Number of days alive outside the ICU at day 28 | 3.5 [0; 17] | 0 [0; 13] | 0.03 |

*SAT* systemic antifungal therapy, *ICU* intensive care unit, *SOFA* sequential organ failure assessment

similar between DE and NoDE groups (Table E3 in ESM).

### Post hoc power analysis

The sample size for the primary objective allowed us to conclude the non-inferiority of SAT de-escalation, in the case of an absolute risk difference of 9 % with a power of 0.8. Details of the post hoc power are given in Table E7 in ESM.

## Discussion

Our causal analysis based on a large prospective observational multicenter study showed that SAT de-escalation in case of suspected or documented IC in non-neutropenic ICU patients occurred in only 22 % of the cases, and did not impact day-28 mortality. DE led to a subsequent and significant decrease in the antifungal consumption. These results remained valid with different subgroups and were confirmed by sensitivity analysis.

Incidence of IC is increasing in ICU patients [27]. Despite the increasing amount of data on IC management, and the development of less toxic antifungal agents, the day-30 and early (before day 8) mortality rates are still increasing over time.

In order to save patients, physicians started antifungals early in case of severe sepsis or shock, without waiting for the definite proof of infection, as it is often delayed. This strategy naturally increased the number of SAT initiated in ICU and is certainly beneficial for ICU patients with documented fungal infections [12]. However, three out of four of the SAT are given without definite proof of fungal infection; this may lead to antifungal overuse with deleterious consequences [12]. Finally, the benefit of this empiric strategy has not been demonstrated in the general ICU

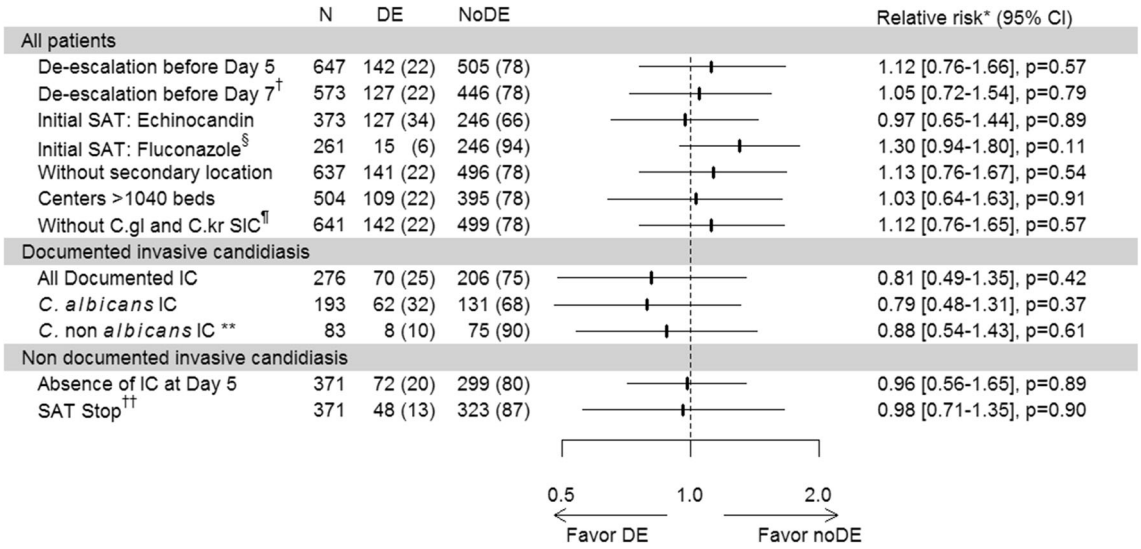


**Fig. 2** Summary of results for primary and secondary outcomes. *DE* de-escalation, *NoDE* no de-escalation, *ICU* intensive care unit, *D5* day 5, *D7* day 7, *SAT* systemic antifungal treatment, *IC* invasive *Candida* infection. **RR* relative risk. If RR < 1, de-escalation is protective for 28-day mortality. If RR > 1, de-escalation is not protective for 28-day mortality. †De-escalation was considered within 7 days after SAT initiation. The estimate was adjusted for SOFA score variation between the SAT start and day 7. §Fluconazole: All patients in the DE group had only stop treatment. ¶Exclusion of patients with suspected invasive candidiasis with *C. glabrata* and *C. krusei*. ***Candida* spp. for the 8 patients in the DE group were *C. glabrata* ($N = 4$), *C. tropicalis* ($N = 2$), *C. parapsilosis* ($N = 1$), and *C. lusitaniae* ($N = 1$). ††DE concerned only patients which switched from all initial SAT to SAT stop within 5 days

population [15, 18]. Furthermore, the overuse of antifungal agents is associated with increased MICs of *Candida* spp. to antifungal drugs [13, 28–31]. In addition, antifungal pre-exposure is associated with clinical [27] and microbiological failures [13, 32] and with breakthrough infections [29, 33]. Antifungal streamlining strategies are therefore fundamental to try to curb the trends.

In the ESCMID guidelines, step-down therapy is recommended only after 10 days for documented infection. In the IDSA guidelines, step-down therapy to fluconazole is considered reasonable for patients who have clinically improved after initial therapy with an echinocandin or polyenes and who are infected with a *Candida* spp. that is likely to be susceptible to fluconazole [20]. However, both the de-escalation rules for the most severe critically ill patients and the stopping rules for SAT started early without proven infection are not defined [19, 20].

For proven invasive candidiasis, three other studies already found that de-escalation is safe in the case of *Candida* spp. sensitive to fluconazole. In a small cost-effectiveness study, de-escalation to oral fluconazole was encouraged for candidemia. Of the 37 episodes of documented candidemia, 27 were commenced on an echinocandin or voriconazole and 19 (70.3 %) were de-escalated to fluconazole on the basis of the intravenous oral switch therapy (IVOST) policy after a mean of 4.6 days, with good results and important cost saving [34].

In the recent ACTION project performed by the Japanese Mycosis Group, clinical failure rate and mortality rate were lower in patients with adherence to step-down oral therapy [22].

An open-label, non-comparative study evaluated an intravenous (i.v.) to oral step-down strategy. Patients with candidiasis were treated intravenously with anidulafungin. After 5 days of i.v. therapy, investigators had the option to step-down to oral azole therapy (fluconazole or voriconazole) if patients met prespecified criteria (ability to tolerate oral therapy; not febrile for more than 24 h; hemodynamically stable; not neutropenic; and documented clearance of *Candida* from the bloodstream). Of the 250 patients enrolled in the mITT population, 102 were switched to oral therapy after a median of 6 days, and clinical response relapse and mortality were similar between patients with early switch and the other patients [21].

Our results confirm previous observations that early de-escalation to azole is possible and safe. We also showed that empiric treatment could be safely stopped after 5 days of SAT therapy in the absence of proven invasive candidiasis.

De-escalation strategy is not explained by severity of organ dysfunction, shock, surgical type of admission, or by the use of other antimicrobial treatments. It occurred less frequently in older patients, for patients in ICU for a longer period of time, or those still under parenteral nutrition.

This study had several limitations. First, it was calibrated to reach a power of 80 % to show an absolute risk difference (ARD) of 9 % between both groups. The study is therefore underpowered to show a smaller ARD,

although still of important clinical relevance. The post hoc power analysis showed that the sample size necessary to reach a sufficient power for subgroup analysis or to show a smaller ARD would need thousands of patients enrolled. This would be unrealistic for a clinical trial.

Secondly, the causal model based on observational data was conducted under the unverifiable assumption of the absence of immeasurable confounders. In this study, there were no measurable time-dependent confounders during the SAT administration. This was a limitation, because SAT de-escalation could be related to the evolution of the patient's state of health during time.

As an example, the beta-D-glucan was not routinely measured within the AmarCAND2 study. However, the potential usefulness of repeated measurements of beta-D-glucan is only suggested in very particular subgroups of ICU patients with complicated abdominal surgery abdominal leakage or acute pancreatitis [35] and lack of specificity and sensitivity in the general ICU population [36].

Third, the reasons leading the investigators to stop SAT were not recorded, although it may have influenced the final results. However, the guidelines for de-escalation were equally followed between DE and NoDE groups.

Last, we cannot be sure that measured confounders occurring between SAT initiation and day 5 that were making physicians prone to de-escalate have been fully taken into account. However, neither the characteristics of the invasive candidiasis nor the SOFA at day 7 or the delta SOFA between SAT initiation and day 7 were different between groups. Furthermore, we analyzed de-escalation at day 7 as an exposure variable; it had no significant effect on the 28-day mortality.

We concluded that, in non-neutropenic critically ill adult patients with proven or suspected IC, SAT de-escalation within 5 days was associated with a decrease in antifungal consumption without apparent deleterious effect on day-28 mortality. De-escalation to fluconazole may be recommended for stabilized patients, with negative blood culture and absence of secondary location for candidiasis. The latter has to be confirmed in randomized control trials.

**Acknowledgments** Members of the independent scientific committee: Olivier Leroy (MD, medical intensivist), Jean-François Timsit (MD, PhD, medical intensivist, epidemiologist), Jean-Pierre Gangneux (MD, PhD, mycologist), Elie Azoulay (MD, PhD, medical intensivist), Jean-Michel Constantin (MD, PhD, anesthesiologist and intensivist), Hervé Dupont (MD, PhD, anesthesiologist and intensivist), Olivier Lortholary (MD, PhD, infectious diseases specialist), Jean-Paul Mira (MD, PhD, medical intensivist), Philippe Montravers (MD, PhD, anesthesiologist and intensivist), Pierre-François Perrigault (MD, anesthesiologist and intensivist). Manuscript preparation: the authors thank Celine Feger (MD; EMIBiotech), who provided assistance in preparing and editing the manuscript and Romain Pirrachio (MD, PhD; University of California, San Francisco) who reviewed statistical analysis.

**Compliance with ethical standards**

**Funding** This work was supported by MSD France, which was the sponsor.

**Conflicts of interest** Authors had full access to the database, and the statistical analyses were conducted by an academic team: Biostatistics Unit, Lille University Hospital, Lille, France, which worked in full independence from MSD.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. J-MC has been a consultant to MSD. HD has been a consultant to Astellas, Gilead, Cubist, Astrazeneca, Merck, and Pfizer. J-PG has been a consultant to Astellas, Gilead, Merck, and Pfizer. DG has benefited from grants of the Principality of Monaco to his research unit. O Leroy has been consultant to Astellas, Gilead, Merck, Novartis, Pfizer, and Sanofi. O Lortholary has been consultant to Gilead Sciences and Novartis and member of the speaker's bureau of Astellas, Basilea, Merck, Pfizer, and Sanofi. J-PM has been a consultant to Astellas, Gilead, MSD, and LFB. PM has been a consultant to Astra-Zeneca, Cubist, MSD, Pfizer, 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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