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Collaborators: Quintard, Hervé

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Original article

# Antifungal therapy for patients with proven or suspected *Candida* peritonitis: Amarcand2, a prospective cohort study in French intensive care units

P. Montravers [1, *], P.F. Perrigault [2], J.F. Timsit [3], J.P. Mira [4], O. Lortholary [5, 6], O. Leroy [7], J.P. Gangneux [8], D. Guillemot [9], C. Bensoussan [10], S. Bailly [11], E. Azoulay [12], J.M. Constantin [13], H. Dupont [14], for the AmarCAND2 Study Group

[1)] *Paris Diderot Sorbonne Cite University, and Anesthesiology and Critical Care Medicine, Bichat-Claude Bernard University Hospital, HUPNSV, AP-HP, Paris, France*
[2)] *Medical-surgical ICU, Montpellier University Hospital, Montpellier, France*
[3)] *Medical ICU, Paris Diderot University, and Bichat University Hospital, HUPNVS, AP-HP, Paris, France*
[4)] *Medical ICU, Cochin University Hospital, HUPC, AP-HP, and Paris Descartes, Sorbonne Paris Cité University, Paris, France*
[5)] *University Paris Descartes, Necker Pasteur Centre for Infectious Diseases, HUNEM, AP-HP, IHU Imagine, Paris, France*
[6)] *Pasteur Institute, National Reference Centre for Invasive Mycoses and Antifungals, CNRS URA3012, Paris, France*
[7)] *Medical ICU, Chatilliez Hospital, Tourcoing, France*
[8)] *Mycology, Rennes University Hospital, Rennes, France*
[9)] *Inserm UMR 1181 « Biostatistics, Biomathematics, Pharmaco-epidemiology and Infectious Diseases » (B2PHI), F-75015 Paris, France*
[10)] *Medical Affairs, Therapy Area Hospital, MSD France, Courbevoie, France*
[11)] *Inserm UMR 1137 – IAME Team 5 – DeSCID: Decision SCiences in Infectious Diseases, Control and Care INSERM/Paris Diderot, Sorbonne Paris Cité University, Paris, France*
[12)] *Medical ICU, Saint-Louis University Hospital, HUSLLFW, AP-HP, Paris, France*
[13)] *Perioperative Medicine Department, Clermont-Ferrand University Hospital, Clermont-Ferrand, France*
[14)] *Surgical ICU, Amiens University Hospital, Amiens, France*

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ABSTRACT

*Objective:* The clinical characteristics and prognosis of patients treated for *Candida* peritonitis (CP) were compared according to the type of systemic antifungal therapy (SAT), empiric (EAF) or targeted (TAF) therapies, and the final diagnosis of infection.
*Methods:* Patients in intensive care units (ICU) treated for CP were selected among the AmarCAND2 cohort, to compare patients receiving EAF for unconfirmed suspicion of CP (EAF/nonCP), to those with suspected secondarily confirmed CP (EAF/CP), or with primarily proven CP receiving TAF.
*Results:* In all, 279 patients were evaluated (43.4% EAF/nonCP, 29.7% EAF/CP and 25.8% TAF patients). At SAT initiation, the severity of illness was similar among EAF/nonCP and EAF/CP patients, lower among TAF patients (median Simplified Acute Physiology Score II (SAPS II) 49 and 51 versus 35, respectively; p 0.001). *Candida albicans* was involved in 67%, *Candida glabrata* in 15.6%. All strains were susceptible to echinocandin; 84% to fluconazole. Echinocandin was administered to 51.2% EAF/nonCP, 49% EAF/CP and 40% TAF patients. At day 28, 72%, 76% and 75% of EAF/nonCP, EAF/CP and TAF patients, respectively, were alive. An increased mortality was observed in patients with a Sequential Organ Failure Assessment (SOFA) score <7 if SAT was delayed by ≥6 days (p 0.04). Healthcare-associated CP (OR 3.82, 95% CI 1.52–9.64, p 0.004), SOFA ≥8 at ICU admission (OR 2.61, 95% CI 1.08–6.34; p 0.03), and SAPS II ≥45 at SAT initiation (OR 5.08, 95% CI 1.04–12.67; p 0.001) impacted the 28-day mortality.
*Conclusions:* In summary, only 56.6% of ICU patients receiving SAT had CP. Most strains were susceptible to SAT. A similar 28-day mortality rate was observed among groups; the late administration of SAT significantly worsened the prognosis of patients with less severe CP. **P. Montravers, CMI 2017;23:117.e1–117.e8**


* Corresponding author. P. Montravers, Département d'Anesthésie-Réanimation, CHU Bichat Claude Bernard, 48 rue Henri Huchard, F-75018 Paris, France.
*E-mail address:* philippe.montravers@aphp.fr (P. Montravers).

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## Introduction

One of the common invasive candidiases is complicated intra-abdominal infection [1–3]. Patients with *Candida* peritonitis (CP) frequently have a recent history of repeated gastrointestinal surgery and/or gastrointestinal perforation.

Several reports in patients with candidaemia demonstrated the positive impact on prognosis and survival of the early initiation of empiric antifungal therapy (EAF) [4–6]. In contrast, data on complicated intra-abdominal infections are lacking. By extension with observations made in candidaemia, an early initiation of systemic antifungal therapy (SAT) is recommended for patients suspected of fungal complicated intra-abdominal infection; however, its benefits are not yet demonstrated. The AmarCAND2 study, a prospective, multicentre, French observational study that enrolled adult patients form intensive care units (ICU) receiving SAT for suspected or proven invasive candidiasis [7], offered a unique opportunity to analyse the effects of an early SAT in this specific subpopulation. Therefore, this post-hoc analysis compared the clinical characteristics and prognoses of patients treated for CP, according to the type of SAT, empiric or targeted, and the final diagnosis of infection.

## Materials and methods

### *Study design and patients*

The cohort of patients presented here was extracted from the AmarCAND2 study database [7]. Consecutive adult patients who underwent abdominal surgery for suspicion of CP during their ICU stay or immediately before (<48 h), had peritoneal samples, and received SAT were analysed. Patients were allocated into three groups: those who received empiric SAT for a suspected but eventually not confirmed CP (Empiric antifungal, EAF/nonCP patients); those who received empiric SAT for secondarily confirmed CP (EAF/CP patients); and those whose SAT was initiated when *Candida* spp. strains were identified into the peritoneal cultures (Targeted antifungal therapy, TAF patients). EAF therapy was defined as a treatment initiated in critically ill patients with risk factors for invasive candidiasis, no other known cause of fever, and clinical assessment of risk factors. TAF was defined as a treatment initiated on the basis of positive *Candida* culture at the time of the SAT initiation.

### *Clinical and mycological data*

Demographic characteristics, underlying diseases, clinical characteristics and severity of illness at ICU admission and at SAT initiation were recorded. Criteria used for building the *Candida* score [8] and the peritonitis score [9] were collected for retrospective calculation.

A positive peritoneal sample was defined as direct examination and/or culture growing *Candida* spp., excluding drain samples. Candidaemia was defined by at least one positive blood culture in the days preceding or following the diagnosis of peritonitis. CP was considered community-acquired if diagnosed within the first 48 h after hospitalization; or nosocomial if diagnosed later. Each local microbiology laboratory performed the routine identification of *Candida* spp. isolates and antifungal susceptibility testing; isolates were classified as susceptible (S), susceptible–dose-dependent (S-DD), or resistant (R). The main marketed methods used referred to CLSI interpretative categories (www.clsi.org).

### *Anti-infective therapy*

Administration of antifungal and antibiotic agents was recorded, as the date and reason(s) for the treatment modifications. Delay for SAT initiation, and its consequences on the outcome were assessed. EAF adequacy was defined as susceptibility of all *Candida* spp. isolates to at least one antifungal administered, whereas inadequacy corresponded to at least one *Candida* spp. strain resistant or S-DD (fluconazole <10 mg/kg/day) to the antifungal received. De-escalation was defined as previously described [10].

### *Outcome*

At the end of therapy, the *Candida* infection outcome, ICU discharge date, and vital status at ICU discharge and at day 28 were collected. Success was defined by the lack of need for a new antifungal or for a surgical treatment not initially scheduled. All the other circumstances were defined as failure, including death occurring more than 48 h after starting SAT and/or premature treatment discontinuation because of an antifungal-related adverse event. Risk factors of death were assessed.

### *Statistical analysis*

Comparisons of clinical characteristics and prognosis were made in patients with a fungal-negative peritoneal fluid culture (EAF/nonCP) and patients with a fungal-positive culture (EAF/CP and TAF). The performances of the *Candida* score and the peritonitis score were assessed in EAF/nonCP versus EAF/CP patients using receiver operating characteristics curves. Finally, the clinical and mycological characteristics and prognosis of EAF/CP patients were compared with those obtained in TAF cases.

Characteristics were stratified for disease severity assessed by Sequential Organ Failure Assessment (SOFA) score (<7 or ≥7).

Variables were expressed as median and interquartile range (IQR) for numerical variables and as frequencies and percentages for categorical variables. Groups were compared using Wilcoxon, chi-square or Fisher's exact tests, as appropriate, with a statistical significance threshold of 0.05. Risk factors for death were assessed by univariate analysis using Wilcoxon/Mann–Whitney test for continuous variables and chi-square or Fisher's exact test for categorical variables followed by a multivariate logistic regression analysis (backward stepwise model). Variables with a $p < 0.1$ were selected for entry into the model. Missing data were replaced by the median value of the population for quantitative data. Adjusted OR and their 95% CI were calculated. Hosmer–Lemeshow test and *c* statistic of the model were calculated. Statistical significance was accepted at the 5% level. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

## Results

### *Patients*

Overall, 279 patients were analysed, including 204 patients with empirical SAT (83 EAF/CP patients and 121 EAF/nonCP patients) and 75 patients with TAF (study flowchart: see Supplementary material, Fig. S1). Characteristics for each group at ICU admission are presented in Table 1.

### *Anti-infective therapy*

Antibacterial therapy was initiated on the day (IQR 0–1) of ICU admission (before ICU admission for 29 (10.4%) patients). Similarly, EAF was administered on the day (IQR 0–1) of collection of surgical samples, while TAF was initiated after 3 (IQR 2–5) days (see Supplementary material, Table S1).

Treatment in EAF/nonCP patients was initiated 1 (IQR 0–5) day after surgical samples, for 5.5 days (IQR 1–48), and almost as often with fluconazole (59/121, 48.8%) or echinocandin (62/121, 51.2%).

At SAT initiation, the severity scores of patients treated with echinocandin were significantly higher than for other patients (47.5 (IQR 35.2–59.7) versus 41 (IQR 27–52); p 0.013, and 8.5 (IQR 4.2–11) versus 5 (IQR 2–8), p <0.0001 for Simplified Acute Physiology Score II (SAPS II) and SOFA score, respectively).

During the initial treatment phase, antifungal agents were administered as monotherapy. A loading dose ≥800 mg of fluconazole was given in 93% and 89% of the patients in the EAF/CP and TAF groups, secondarily decreased to 400 mg daily in all but five patients (see Supplementary material, Table S1).

### *Candida score and peritonitis score*

The *Candida* score and the peritonitis score were calculated among all EAF/nonCP and EAF/CP patients. *Candida* colonization was assessed in 16 (13.2%) EAF/nonCP patients and 6 (7.2%) EAF/CP patients (p 0.17). The area under the curve for the *Candida* score was 0.412 (95% CI 0.335–0.490) and that for the peritonitis score was 0.572 (95% CI 0.491–0.652) (Fig. 1).

### *Mycological data*

Direct examination was positive for *Candida* in 34 patients (21 EAF/CP and 13 TAF cases), and identification was obtained after 2 (IQR 2–4) days, whereas susceptibility profile was available after 6 (IQR 4–10) days.

Overall, 179 *Candida* strains were cultured from peritoneal samples (*Candida albicans* in 61/96 (64%) isolates for EAF/CP patients and 59/83 (71%) for TAF patients; see Supplementary material, Table S2). Mixed bacterial and fungal cultures were observed for 45 (60%) samples in the TAF patients (data not available for EAF patients).

Susceptibility profile was obtained for 125 (70%) peritoneal isolates, including 79 *C. albicans* strains. According to the result of local laboratories, all *C. albicans* strains were susceptible to fluconazole, whereas only 8/20 (40%) of the tested strains of *Candida glabrata* were susceptible to fluconazole. Overall, 100% of *Candida*

**Table 1**
Characteristics at intensive care unit admission and at the time of initiation of the antifungal therapy

| | Empiric antifungal therapy/ Non-confirmed CP $n = 121$ | Empiric antifungal therapy/ Confirmed CP $n = 83$ | Targeted antifungal therapy $n = 75$ | p value |
|---|---|---|---|---|
| Female gender, *n* (%) | 56 (46) | 40 (48) | 28 (37) | 0.34 |
| Age, year, median (IQR) | 64 (55–73) | 65 (56–75) | 64 (52–77) | 0.84 |
| Body mass index ≥35 kg/m$^2$, *n* (%) | 23 (19) | 16 (19) | 8 (11) | 0.87 |
| Underlying disease | | | | |
| Cardiovascular disease, *n* (%) | 21 (17) | 19 (23) | 21 (25) | 0.02 |
| Immunosuppression, *n* (%) | 7 (6) | 4 (5) | 7 (9) | 0.47 |
| Long-term steroid therapy, *n* (%) | 6 (5) | 2 (2) | 2 (3) | 0.56 |
| Diabetes, *n* (%) | 12 (10) | 15 (18) | 13 (17) | 0.18 |
| Renal dysfunction, *n* (%) | 16 (13) | 12 (14) | 18 (24) | 0.12 |
| Cancer, *n* (%) | 32 (26) | 29 (35) | 20 (27) | 0.37 |
| Surgery within last 3 months, *n* (%) | 76 (63) | 51 (61) | 40 (53) | 0.39 |
| Surgery above transverse mesocolon, *n* (%) | 50 (41) | 46 (55) | 27 (36)[a] | 0.03 |
| Delay of ICU admission, days, median (IQR) | 3 (0–7) | 1 (0–8) | 2 (0–9) | 0.09 |
| Emergent surgical admission in ICU, *n* (%) | 105 (87) | 79 (95) | 71 (95) | 0.06 |
| Healthcare-associated infection, *n* (%) | 62 (51) | 43 (52) | 51 (68) [a] | 0.04 |
| Severity on admission | | | | |
| SAPS II, median (IQR) | 50 (36–64) | 55 (45–64) | 48 (37–58) [b] | 0.02 |
| SOFA, median (IQR) | 7 (5–9) | 8 (6–10) | 8 (5–10) | 0.91 |
| Cardiovascular failure, *n* (%)* | 91 (75) | 56 (67) | 50 (67) | 0.33 |
| Respiratory failure, *n* (%)* | 51 (42) | 26 (31) | 40 (53) [b] | 0.002 |
| Renal failure, *n* (%)* | 16 (13) | 25 (30) | 22 (30) | 0.005 |
| Severity on the day of initiation of antifungal therapy | | | | |
| SAPS II, median (IQR) | 49 (37–61) | 51 (42–66) | 35 (26–48) [b] | 0.001 |
| SOFA, median (IQR) | 9 (6–12) | 8 (5–10) | 5 (2–8) [b] | 0.001 |
| Cardiovascular failure, *n* (%)* | 93 (77) | 57 (69) | 25 (33) [b] | 0.0001 |
| Respiratory failure, *n* (%)* | 59 (49) | 24 (29) | 12 (16) | 0.053 |
| Renal failure, *n* (%)* | 19 (16) | 15 (18) | 12 (16) | 0.729 |
| Fever >38°C, *n* (%) | 46 (38) | 29 (35) | 14 (19) | <0.014 |
| Septic shock, *n* (%) | 92 (76) | 55 (66) | 20 (27) [b] | 0.001 |
| Mechanical ventilation, *n* (%) | 109 (90) | 71 (86) | 42 (56) [b] | 0.001 |
| Central venous catheter, *n* (%) | 120 (99) | 79 (95) | 72 (96) | 0.19 |
| Total parenteral nutrition, *n* (%) | 61 (50) | 35 (42) | 55 (73) [b] | 0.001 |
| Ongoing antibiotic therapy, *n* (%) | 107 (88) | 76 (92) | 75 (100) [b] | 0.01 |
| Steroid therapy, *n* (%) | 34 (28) | 14 (17) | 9 (12) | 0.02 |
| Renal replacement therapy, *n* (%) | 29 (24) | 22 (27) | 17 (23) | 0.84 |
| Blood transfusion since admission, *n* (%) | 53 (44) | 33 (40) | 35 (47) | 0.61 |
| Procalcitonin, mg/L, median (IQR) [c] | 3.9 (0.4:14.8) | 2.4 (0.5–19.2) | 2.9 (0.8–17.5) | 0.45 |
| C-Reactive protein, mg/mL, median (IQR) [d] | 162 (109:242) | 218 (141–273) | 114 (86–294) [b] | 0.01 |

The p values presented in the right column correspond to the comparison between the three groups. In case of significant difference, a comparison was made between empiric (EAF/CP) and targeted therapy (TAF).
Abbreviations: CP, *Candida* peritonitis; IQR, interquartile range; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.
Patients allocation in each group were reviewed by study experts (PM and HD).
* Organ failure according to the definitions of the SOFA score.
[a] p <0.05 between empiric and targeted therapy.
[b] p <0.01 between empiric and targeted therapy.
[c] Numbers of available data for procalcitonin levels: $n = 28$ for TAF patients, 35 for EAF/CP, and 48 for EAF/nonCP.
[d] Numbers of available data for C-reactive protein levels: $n = 30$ for TAF patients, 41 for EAF/CP, and 53 for EAF/nonCP.

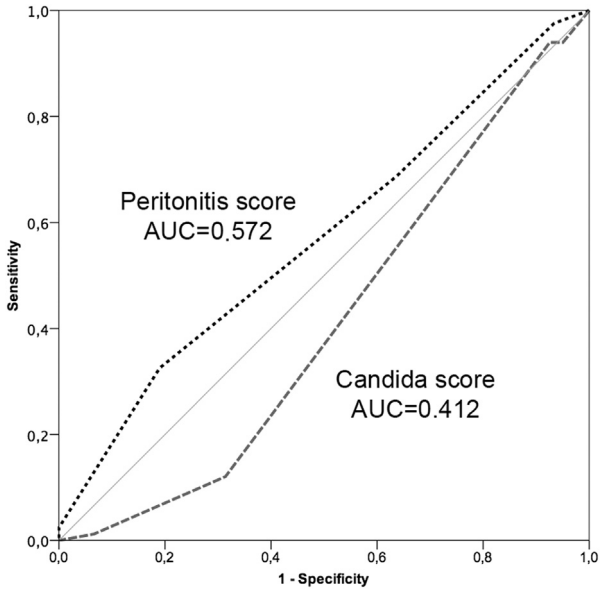


**Fig. 1.** Receiver operating characteristic curve of the area under the curve of the predictive performance of each score, *Candida* score and peritonitis score, according to the confirmed diagnosis of *Candida* peritonitis.

spp. strains were susceptible to echinocandin, 84% to fluconazole, 96% to voriconazole and 100% to amphotericin B.

### *Antifungal therapeutic adjustments*

Adequacy of SAT was reached in 73 (88%) EAF/CP and 69 (92%) TAF patients. Its inadequacy was mainly related to low susceptibility of five *C. glabrata* strains and to three patients with *Candida krusei* treated with fluconazole. In addition, the adequacy of antibacterial therapy was achieved in 65 (87%) TAF patients, and in 28/33 (85%) EAF/CP patients with available mycological results.

The initial SAT was modified in 40 (48%) EAF/CP and 27 (36%) TAF patients, after 5 (IQR 3–7) and 3 (IQR 2–4) days, respectively. Changes were mainly related to the species isolated (52 cases, including 37 EAF/CP patients) and to their susceptibility profile (34 cases, including 23 EAF/CP patients), and rarely to clinical worsening (four cases (including two EAF/CP patients)) (see Supplementary material, Table S3). During EAF therapy, de-escalation was reported in 30 (36%) patients, and escalation in eight (10%) patients. During TAF therapy, de-escalation was observed in 19 (25%) cases and escalation in eight (11%) cases. The SOFA score at D7 after SAT initiation was similar among patients who underwent de-escalation and those who did not (3 (IQR 2–5.75) versus 3.5 (IQR 1–6), respectively, p 0.529).

Additional surgical procedures were performed in 11 cases, 6 (IQR 2–8) days after initial surgery and 1 (IQR 0–5) days after SAT initiation.

### *Outcome*

At day 28, 81 (66.9%) EAF/nonCP patients, 59 (71.0%) EAF/CP patients and 54 (72.0%) TAF patients were alive (p 0.79) (Table 2). Overall, neither the delay of antifungal therapy initiation (Fig. 2a) nor the SAT adequacy seems to influence the outcome among the two groups of patients with proven CP, except for the less severely ill patients (SOFA score <7) who displayed an increased mortality in the case of delayed therapy (p 0.04) (Fig. 2b).

In the EAF/CP group, 13 clinical failures, all associated with death, were reported after 5 (IQR 2–18) days in median (including three early deaths within 24 h after SAT initiation). Among the five TAF patients who experienced clinical failure, four died after 4 (IQR 2.5–4.5) days in median. In addition, recurrence of infection was observed in three patients (including two TAF patients) who subsequently died. The risk factors for the day-28 mortality according to the univariate analysis are presented in Table 3, and those of therapeutic success are shown in Table S4 (see Supplementary material). In multivariate analysis, the risk factors independently associated with death are detailed in Table 3 (Wald $\chi^2 = 23.88$, p <0.0001; Hosmer–Lemeshow test = 3.71; p = 0.71; C statistic = 0.75 (95% CI 0.66–0.84).

## Discussion

The results presented here focus on the subgroup of ICU patients suspected of having *Candida* peritonitis extracted from a large prospective observational study on invasive candidiasis [7]. Patients with a non-confirmed diagnosis of CP (EAF/nonCP) did not significantly differ from those with a secondarily proven CP receiving EAF (EAF/CP). The *Candida* and peritonitis scores

**Table 2**
Clinical parameters and outcome in the groups of patients who received empiric antifungal therapy, for suspicion of *Candida* peritonitis, either subsequently proven or not, and those receiving targeted therapy for proven *Candida* peritonitis

| | Empiric antifungal therapy Non confirmed CP $n = 121$ | Empiric antifungal therapy Confirmed CP $n = 83$ | Targeted antifungal therapy $n = 75$ | p value |
|---|---|---|---|---|
| SOFA score at D7, median (IQR) | 5 (1–9) | 3 (1–8) | 3 (1–5) | 0.02 |
| Clinical outcome [a] | | | | 0.02 |
| Cured, *n* (%) | 78 (64) | 59 (71) | 56 (75) | |
| Failure, *n* (%) | 9 (7) | 14 (17) | 7 (9) | |
| Undetermined, *n* (%) | 34 (28) | 10 (12) | 12 (16) | |
| Alive at day 28, *n* (%) | 81 (67) | 59 (71) | 54 (72) | 0.79 |
| Discharged alive from the ICU, *n* (%) | 85 (70) | 60 (72) | 58 (77) | 0.49 |
| Discharged alive from the hospital, *n* (%) | 69 (57) | 51 (61) | 44 (59) | 0.85 |
| Duration of antifungal therapy (survivors), median (IQR) | 6 (4–14) | 17 (13–21) | 14 (10–21) | <0.001 |

The p values presented in the right column correspond to the comparison between the three groups. In case of significant difference, a comparison was made between empiric (EAF/CP) and targeted therapy (TAF).
Abbreviations: CP, *Candida* peritonitis; ICU, Intensive Care Unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.
[a] Clinical outcome definitions: success was defined by the lack of need for a new antifungal or for a surgical treatment not initially planned for the initial infection. Failure was defined by the persistence of the initial infection signs requiring a change of antifungal therapy or an unplanned surgical intervention, the reappearance of the initial infection signs, or death occurred more than 48 h after the start of therapy and/or premature treatment discontinuation due to an antifungal-related adverse event. Undetermined cases were patients with early discharge or early death, or patients lost to follow up.

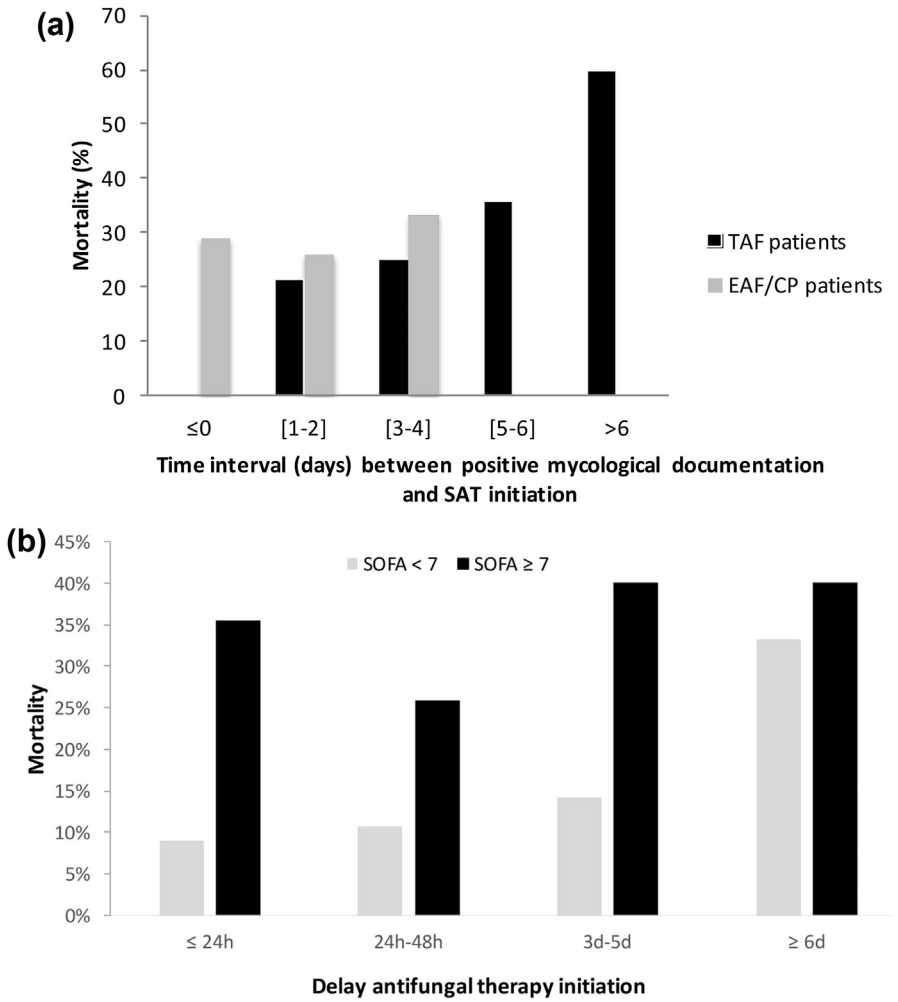


**Fig. 2.** Mortality rate according to the time interval between the positive documentation of the fungal infection and the systemic antifungal therapy initiation, for the patients with targeted antifungal therapy (TAF) versus patients with empiric antifungal therapy /*Candida* peritonitis EAF/CP) (a), or according to the severity of illness reflected by the Sequential Organ Failure Assessment (SOFA) (b). Positive documentation of the fungal infection is defined by the identification of the fungal species involved.

insufficiently discriminated EAF/nonCP patients from EAF/CP patients. Low rates of fluconazole-resistant strains were reported, except for *C. glabrata*, which was the most frequent non-*albicans* yeast. Initial SAT was modified in 48% EAF/CP patients and 36% TAF patients, mainly for a better adjustment to the pathogen and its susceptibility profile. Among the three groups, the day 28 survival rate was not significantly different, and the overall outcome was similar. A delayed initiation of SAT did not impact the prognosis for severely ill patients (SOFA $\geq$7), but it increased the mortality among less severely ill patients. Healthcare-associated infection, high SOFA score at ICU admission, and high SAPS II score at SAT initiation were identified as risk factors of death.

A large proportion of patients suspected of having CP unduly received empiric SAT. This previously reported overuse of SAT illustrates the difficulty of discriminating true infection from colonization [11]. In our non-selected surgical population, the value of the peritonitis score [12] and the *Candida* score [13] was deceptive. The scores were built to discriminate patients requiring early initiation of SAT. However, most of the patients admitted in emergency and/or transferred from another institution do not have any fungal mapping.

*Candida albicans* was the most frequent causative yeast, and *C. glabrata* was the leading non-*albicans* pathogen, as usually observed in intra-abdominal infections [1,12,14–19]. The recent EUCAST recommendations considering *C. glabrata* as resistant to fluconazole were not available at study initiation [20]. Interestingly, several patients receiving fluconazole had an uneventful outcome, suggesting that these organisms were probably more colonizing than pathogenic strains.

In contrast with the results of the first AmarCAND study, local laboratories did not report any strains of fluconazole-resistant *C. albicans* [21]. In addition, we did not observe any echinocandin-resistant strains [22]. In view of our data, the extensive use of echinocandins in surgical patients suspected of CP could be questioned. The low number of cases did not allow us to look for clinical criteria to identify *C. glabrata* infections, probably the best indication of echinocandins in this subpopulation.

The pharmacokinetic issues were not addressed in the AmarCAND2 study. Recent data have suggested that the plasma trough concentrations of fluconazole and echinocandins were highly variable and possibly quite low in ICU patients [23,24]. Similarly, the rare peritoneal measurements of antifungal agents showed a large variability, and, for micafungin, a peritoneal fluid:plasma ratio of 0.3 [24]. Overall, the daily dose of fluconazole should be considered cautiously, as some patients may require daily doses >200 mg [23].

The need for an early adequate SAT in CP is another interesting point of debate. The deleterious impact of delayed SAT initiation has never been demonstrated for *Candida* intra-abdominal

**Table 3**
Risk factors for mortality at day 28, odds ratio and 95% CI

| | Dead ($n = 37$) | Survivors ($n = 113$) | OR | 95% CI | p value | Adjusted OR | 95% CI | P value |
|---|---|---|---|---|---|---|---|---|
| Female gender, *n* (%) | 15 (41) | 50 (44) | 1.164 | (0.547–2.474) | 0.692 | | | |
| Age, years, median (IQR) | 73 (59–81) | 63 (53–74) | 2.852 | (1.329–6.117) | 0.006 | | | |
| BMI ≥35 kg/m$^2$, *n* (%) | 4 (11) | 17 (15) | 0.684 | (0.214–2.180) | 0.597 | | | |
| Initial septic surgery, *n* (%) | 33 (89) | 82 (73) | 3.118 | (1.020–9.529) | 0.044 | | | |
| Empiric antifungal therapy, *n* (%) | 19 (51) | 59 (52) | 0.966 | (0.459–2.030) | 0.972 | | | |
| Initial surgery above transverse mesocolon, *n* (%) | 13 (35) | 57 (50) | 0.532 | (0.246–1.148) | 0.105 | | | |
| Nosocomial infection, *n* (%) | 27 (73) | 63 (56) | 2.142 | (0.948–4.841) | 0.063 | 3.82 | (1.52-9.64) | 0.004 |
| Ongoing antibiotic therapy, *n* (%) | 35 (95) | 109 (96) | 0.642 | (0.112–3.657) | 0.636 | | | |
| Severity criteria on admission | | | | | | | | |
| SAPS II score, median (IQR) | 58 (48–68.5) | 49 (38–59.5) | 2.165 | (1.003–4.675) | 0.046 | | | |
| SOFA score, median (IQR) | 9 (57–11) | 8 (5–10) | 2.136 | (1.003–4.549) | 0.046 | 2.61 | (1.08-6.34) | 0.03 |
| Severity on the day of initiation of antifungal therapy | | | | | | | | |
| SAPS II score, median (IQR) | 52 (42.5–63) | 42 (30–54) | 3.656 | (1.617–8.266) | 0.002 | 5.08 | (2.04-12.67) | 0.001 |
| SOFA score, median (IQR) | 9 (5.5–11.5) | 6 (3–9) | 2.895 | (1.335–6.275) | 0.007 | | | |
| Cardiovascular failure, *n* (%) | 25 (68) | 54 (48) | 2.276 | (1.042–4.970) | 0.036 | | | |
| Septic shock, *n* (%) | 22 (59) | 50 (44) | 1.848 | (0.869–3.927) | 0.107 | | | |
| Severe sepsis, *n* (%) | 10 (27) | 49 (43) | 0.483 | (0.214–1.093) | 0.077 | | | |
| Renal replacement therapy, *n* (%) | 17 (46) | 22 (19) | 3.515 | (1.584–7.799) | 0.001 | 1.33 | (0.48-3.72) | 0.14 |
| Blood transfusion since admission, *n* (%) | 23 (62) | 45 (40) | 2.482 | (1.156–5.328) | 0.017 | 1.84 | (0.81-4.32) | 0.15 |
| Mycological characteristics | | | | | | | | |
| Pure fungal infection,[a] *n* (%) | 29 (78) | 101 (89) | 0.430 | (0.160–1.153) | 0.099 | | | |
| Presence of non-albicans *Candida*, *n* (%) | 12 (32) | 36 (32) | 1.026 | (0.464–2.271) | 0.948 | | | |
| Presence of *Candida glabrata*, *n* (%) | 9 (24) | 19 (17) | 1.590 | (0.647–3.904) | 0.334 | | | |
| Therapeutic characteristics | | | | | | | | |
| Initial therapy using azoles, *n* (%) | 16 (43) | 63 (56) | 0.604 | (0.285–1.278) | 0.185 | | | |
| Initial therapy using echinocandins, *n* (%) | 21 (57) | 50 (44) | 1.653 | (0.782–3.497) | 0.186 | | | |
| Adequate initial antifungal therapy, *n* (%) | 35 (95) | 100 (88) | 2.275 | (0.488–10.587) | 0.360 | | | |
| Antifungal de-escalation, *n* (%) | 11 (30) | 34 (30) | 0.983 | (0.436–2.213) | 0.967 | | | |
| Initial success, *n* (%) | 9 (24) | 100 (88) | 0.041 | (0.016–0.107) | <0.0001 | | | |

Odds ratio: univariate analysis. Adjusted Odds ratio: multivariate analysis.
Abbreviations: BMI, body mass index; IQR, interquartile range; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.
[a] Pure fungal infection was infection solely due to fungi, without bacterial involvement.

infection [1,25]. Among our patients, no relationship could be evidenced, except for the less severely ill patients (SOFA <7) in case of extremely delayed SAT initiation (≥6 days). These observations need to be confirmed in a specific study among patients with CP.

The adequate duration of SAT for patients with CP is another unsolved issue. The IDSA guidelines did not provide any recommendations for SAT duration [26]. Similarly, ESCMID recommendations did not individualize fungally complicated intra-abdominal infection [27]. Based on the high rates of recurrence and relapse in CP, experts recommended long duration of SAT, around 2–3 weeks [29]. In our study, patients received SAT for 17 days (median).

Our observations have several limitations. First, the low number of patients and the mixed population of community-acquired and healthcare-associated infections is an issue for results interpretation, as illustrated in a case–control study, which showed a pathogenic role of *Candida* only in nosocomial peritonitis [30]. Our low number of cases did not enable us to extrapolate our hypotheses on specific subpopulations. Biomarkers such as BD-Glucan were not routinely measured in France when the AmarCAND2 study was conducted. In ICU patients, the usefulness of repeated BD-Glucan measurements is suggested for discriminating colonization from infection cases [31]. Overall, our data reflect 'real-life' and explain the high proportion of unjustified SAT. Our study did not assess the adequacy of source control, although it could have contributed to explain therapeutic failure [32].

## Conclusion

From the large prospective AmarCAND2 study on invasive candidiasis in ICU patients [7], we specifically evaluated patients receiving SAT for suspected or proven CP. The *Candida* score and the peritonitis score did not discriminate patients with CP from others. The deleterious impact on survival of delaying SAT initiation is limited to delays >5 days in less severely ill patients. A prospective study addressing this specific issue is required, as all recent guidelines emphasized the need for an early and adequate SAT [26,28,33]. The key factors independently associated with 28-day mortality were mostly related to the patient illness severity, and the initial therapeutic success; patients with previous septic abdominal surgery, as those with health-care-associated CP, were also at higher risk of mortality. The improvement of CP management among ICU patients requires further studies to better characterize patients at risk of poor prognosis.

## Transparency Declaration

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 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 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 symposia 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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## Appendix A. Supplementary material

Additional Supporting Information may be found in the online version of this article can be found at http://dx.doi.org/10.1016/j.cmi.2016.10.001.

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