Empiric antifungal and outcome in ICU patients.

Antifongique empirique et évolution chez les patients de réanimation.

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RÉSUMÉ

Introduction: Le traitement de la candidose invasive (CI) demeure un défi en réanimation. L'administration tardive des antifongiques étant un facteur indépendant de mortalité. La prescription irraisonnable de ces agents est une source d'émergence de souches résistantes.

Objectif: évaluer l'effet d'un traitement antifongique empirique (TAFE) sur la survie à J 28 et sur la survenue de candidémie chez les patients septiques sans infection candidosique prouvée.

Méthodes: étude de cohorte monocentrique, rétrospective sur 8 ans, comparant deux bras de patients septiques non neutropéniques sans infection fongique prouvée selon l'administration ou non d'un TAFE. Les 2 critères de jugement sont la mortalité à 28 jours et l'apparition de la candidémie. L'analyse a été ajustée sur le score APACHE II, le Candida score, la ventilation invasive et le cathétérisme central.

Résultats: 247 patients ont été inclus (groupe TAFE, n = 125 et groupe non TAFE, n = 122). Aucune amélioration de la survie à 28 jours n'a été trouvée. Ces résultats étaient concordants à l'analyse brute et après ajustement sur les facteurs mentionnés ci-dessus. Aucun effet préventif sur la survenue de candidémie. Un effet bénéfique du TAFE sur la survie a été observé chez des patients ayant un score APACHE II <16: OR= 0,68; IC 95% [0,53-0,87]; p=0,002.

Conclusions: aucun effet bénéfique d'un TAFE sur la survie à 28 jours ni sur la prévention de l'apparition d'une candidémie chez les patients septiques non neutropéniques de réanimation. Chez les patients ayant un score APACHE II < 16, il y avait un effet bénéfique sur la survie.

Mots-clés

Antifongique; thérapie empirique; candidémie; septicémie nosocomiale; survie

SUMMARY

Background: The management of invasive candidiasis (IC) remains a major challenge in intensive care units (ICU). On the one hand, it becomes admitted that delayed antifungal is an independent mortality factor. In the other hand, the unreasonable administration of antifungal agents is implicated in emergence of resistant Candida strains.

Aim: to evaluate whether empirical antifungal therapy (EAFT) improves survival at day 28 and prevents a new episode of candidemia in septic patients without proven Candida infection.

Methods: a 8-years retrospective double cohort, monocentric study, comparing two arms of ICU non neutropenic septic patients without proven fungal infection according to administration or not of an EAFT. The primary outcome was the 28-day mortality and the second was the occurrence of candidemia. The analysis was adjusted on Acute Physiology And Chronic Health Evaluation II (APACHE II) score, Candida score, invasive ventilation and central catheterisation.

Results: 247 patients were included (EAFT group, n=125 and non EAFT group, n=122). No improvement of 28-day survival was found. These results were in accordance both in crude analysis and after adjusting on factors mentioned above. No preventing effect on a new episode of candidemia. Nevertheless, a beneficial effect of EAFT on survival was found in patients with an APACHE II score<16: OR=0.68; CI 95% [0.53-0.87]; p=0.002.

Conclusions: no beneficial impact of an EAFT on 28- day survival neither in preventing the occurrence of candidemia in non neutropenic septic critically patients. In patients with APACHE II score less than 16, there was a beneficial effect on survival.

Key-words

Antifungal; empiric Therapy; candidemia; nosocomial sepsis; survival

INTRODUCTION

In critically ill patients, invasive candidiasis (IC) incidence's is growing and this is explained as a result of invasive procedures and the over-use of antibacterial and antifungal agents (1-3). Despite the development of effective and safer drugs, IC and candidemia remain associated with high mortality, namely when it is complicated by septic shock (4-7).

IC stills a major challenge in critically ill patients with unresolved sepsis. Indeed, the diagnosis of IC is usually late and confirmed by a positive blood culture for *Candida* species but the diagnosis of IC without candidemia is less evident. Recent guidelines recommend research of mannan antigen/ antibody with especially an excellent negative predictive value (8,9). But this is not always easy to reveal the IC. Furthermore, biomarkers such beta-D-glucan, not available at all the time.

Therefore, antifungal are increasingly used as empirically, mainly in patients at risk for IC or patients with unresolved sepsis. Some tools may help in selection of patients with high risk of IC, such the Candida score (10,11). The optimal management of *Candida* species infections includes an earlier selection of patients at risk of IC, a control of the infection source, and the administration of appropriate antifungal (7-9,12,13). Several recent investigations demonstrated that inappropriate empiric or delayed antifungal therapy was related to mortality in septic shock due to Candida infection (14-16). Unreasonable administration of antifungal led to the emergence of non-albicans *Candida* infections and resistant *candida* strains (17,18).

The impact of an empiric antifungal therapy (EAFT) on prognosis was suggested by several studies (19-21), but without formal proof.

We aimed to evaluate whether EAFT improved survival and reduced the number of ICU acquired candidemia in septic critically ill patients without proven *Candida* infection.

METHODS

Study Design and Location: it was monocentric, retrospective double cohort study conducted in a medical ICU with the collaboration of mycology and parasitolgy department over 8-years period (January 2008–December 2015) in the university hospital center of la Rabta.

Patients and Data Collection: non neutropenic patients with an ICU stay of more than seven days who developed a sepsis without documented bacterial or fungal infection were eligible for inclusion in our study. Patients who received a targeted antifungal for a proven Candida infection and those with neutropenia (neutrophil count of less than 500/mm3) were excluded. Thus, two groups were compared according to the administration or not of an EAFT (EAFT versus non EAFT).

Patient specific baseline characteristics as well as the follow-up of clinical, biological and microbiological data were collected from the hospital medical record. The predisposing factors of invasive candidiasis were collected as well as the outcome criteria (length of stay in ICU and 28 day mortality). The subsequently documented infections with the isolated pathogens and received antibiotics were also recorded.

Definitions: To be included in the analysis, patients had to meet criteria for sepsis, severe sepsis or septic shock without documented fungal infection. Sepsis, severe sepsis or septic shock criteria were based on definitions of Surviving Sepsis Campaign 2012 (22). The Timing of EAFT was determined from the interval between the onset of sepsis or septic shock and administration of the first intravenous dose of antifungal. The prescription was considered empirical when it occurred within 24 hours of the onset of sepsis or septic shock. Confounding factors that we have adjusted our analysis were: APACHE II score, Candida score, invasive ventilation and central catheterisation. The Acute Physiology and Chronic Health Evaluation (APACHE) II was calculated based on clinical data present during the 24 hours of the beginning of sepsis (23).

Outcome assessment: The primary end point was survival at day 28. The stratified analysis was assessed in predefined subgroups (APACHE II <16 vs > 16, candida score <3 or ≥3, mechanical ventilation vs not, central catheterization vs not). The secondary end point was the number of candidemia.

Statistical analysis:

***Sample Size Calculation*:** As previously published, the mortality varied from 30 to 50% (19,20,24-26) in invasive candidiasis if not treated earlier, and the candidemia-related mortality

in case of early treatment would be 12% instead of 35% when the treatment is delayed (current practice, equivalent

to a reduction percentage of 65% (7,21). We estimated that 124 evaluable patients per group were needed to take into account the expected the decreasing of mortality of 65% with a two-sided α risk of 5% and a power of 80% to compute sample size,.

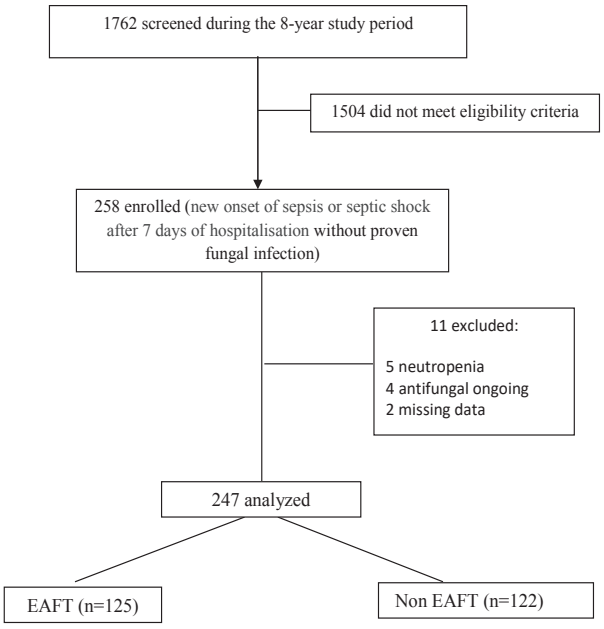
Quantitative variables were expressed by means or medians and compared by the Student t-test or the Mann-Whitney U-test, as appropriate. Qualitative data were expressed as percentages and compared by the χ^2 or Fisher's Exact test, as appropriate. The measures of association between the EAFT and the 28-day survival were expressed by the odds ratio. The adjustment on predefined covariates was performed by the method of Mantel Hansel. The survival rates over time were represented by the Kaplan-Meier survival curves and compared by the log-rank test. The confidence interval was fixed at 95%. Data processing was done using SPSS Version 20 software.

Ethics statement: This study was approved by our local institutional review boards, and written patient consent was not required because of the retrospective nature of this study.

RESULTS

Patient's clinical characteristics:

During the study period, 1762 patients were admitted to the medical ICU and among them 247 have met our inclusion criteria (EAFT group, n=125 and non EAFT group: n=122), the distribution of studied population is displayed in figure 1. Our groups were comparable on demographic criteria, APACHE II score, co-morbidities and admission reason. The major identified predisposing factors of invasive candidiasis were central catheter; mechanical ventilation; previous antimicrobial therapy and less frequent the parenteral nutrition and hemodialysis (Table 1). The all five patients who had abdominal surgery received an EAFT. No difference was shown between groups regarding the risk factors, mainly the *Candida* colonisation before inclusion (36.8% versus 26.2%, p=0.1). The mean *Candida* score was superior in the intervention group without a real difference (4.33 ± 0.5 versus 3.09 ± 1.3, p=0.08). The prescribed antibiotics were directly against the multidrug resistant bacteria and were administered similarly between the groups. The median days on mechanical ventilation and ICU stay did not differ (Table 1).



EAFT: empiric antifungal therapy

Figure 1 : Patient's flow chart

Infectious data:

The microbiological follow up showed that a documented infection was identified among 81.6% of the intervention group and 78% of control group. The median delay required to the microbiological documentation was at 4 versus 5 days in the intervention and control groups respectively. The observed infections were classified in bacterial (51.2% vs 48.5%, p=1), fungal (30.4% vs 29.5%, p=0.8) and not documented infection (18.4% vs 22%, p=0.96) in the EAFT and non EAFT groups respectively. The most frequent infection was ventilator associated pneumonia (VAP) and the most common isolated pathogens were *Acinetobacter baumannii* (EAFT: 44% and non EAFT: 52%) and *Candida albicans* (EAFT: 63% and non EAFT: 58%). The distribution did not differ between the study groups.

When considering the total number of screened patients, the overall incidence of *Candida* infection was 21.5 per 1000 admissions for candidemia and 20.4 per 1000 admissions for *Candida* colonisation. No cases of complicated intra-abdominal infections were diagnosed.

Effect on survival of EAFT:

In our series, we did not find an improvement in 28- day

Table I: Patient's baseline characteristics

	EAFT (n=125)	Non EAFT (n=122)	P value
Age, years (mean + SD)	50 ± 16	52 ± 15	0.21
Male, n (%)	64 (51.2%)	67 (55%)	0.61
APACHE II score at inclusion (mean + SD)	17.9 ± 6	18.4 ± 7.5	0.58
SOFA score at inclusion (mean + SD)	8.3 ± 3.6	8.7± 4.1	0.43
Admission reason: n (%)			
Respiratory distress	57 (45.6%)	53 (43.3%)	1
Hemodynamic failure	38 (30.4%)	28 (23%)	0.68
Neurological causes	19 (15.2%)	26 (21.3%)	0.5
Metabolic Disorders	7 (5.6%)	15 (12.3%)	0.1
Others	4 (3.2%)	-	-
Co-morbidities: n (%)			
Diabetes,	35 (28%)	31 (25.4%)	0.72
Chronic respiratory failure,	26 (21%)	19 (16%)	0.16
Cardiovascular disease,	16 (12.8%)	18 (15%)	0.24
Chronic renal failure,	13 (10.4%)	6 (5%)	0.09
Neurological disease	12 (9.6%)	13 (10.6%)	0.17
Systemic disease,	10 (8%)	8 (6.5%)	0.36
Neoplasic diseases,	5 (4%)	2 (1.7%)	0.12
Endocrine disorders,	6 (4.8%)	8 (6.5%)	0.58
Mechanical ventilation, n (%)	95 (76%)	96 (78.7%)	0.65
Central catheter, n (%)	113 (90.4%)	104 (85.2%)	0.24
Previous antimicrobial therapy, n (%)	99 (79.2%)	78 (64%)	0.1
Parenteral nutrition, n (%)	80 (64%)	64 (52.4%)	0.5
Candida colonisation at inclusion*	46 (36.8%)	32 (26.2%)	0.1
Abdominal surgery	5 (4%)	0	
Extracorporeal hemodialysis	9 (7.2%)	7 (5.7%)	0.38
Candida score, mean	4.33 ±0.5	3.09±1.3	0.08
Prescribed antibiotics:			
Imipinem, colistin	56 (44.8%)	63 (51.6%)	0.59
Imipinem, colistin, *vancomycine*	45 (36%)	32 (26.3%)	0.16
Colistin, tigecyclin	17 (13.6%)	14 (11.5%)	1
Others	7 (5.6%)	13 (10.6%)	0.1
Mechanical ventilation days; mean	14.96 ± 6.6	15.03 ± 7.3	0.95
Length of stay in ICU; mean	24 ± 17.2	25.9 ± 13	0.45
28 days-Mortality, n (%)	45 (36%)	49 (40.2%)	0.51

EAFT: empiric antifungal therapy, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment. ICU: intensive care unit, SD: standard deviation, *: ca

survival both in crude analysis and stratified analysis OR = 0.94; CI 95% [0.77-1.15]; p = 0.34 and OR= 0.54; CI 95% [0.7-1.95]; p= 0.63. However, a protective impact of the EAFT on 28 day-survival was found in the subgroup of moderate severity with an APACHE II score lower than 16: OR= 0.68; CI95% [0.53-0.87] and p=0.002 (Table 2).

The mortality in the EAFT group was 36% and that of non EAFT group was 40.2% without significant difference (p=0.51). Similarly, survival times were comparable to 28 days with median survival time of 25 days [21-28] in EAFT group and 22 days [19-24] in non EAFT group. The survival analysis using the Kaplan-Meier curves tended to significance but without real difference between the two groups (p = 0.07) (Figure 2).

Table 2 : **I**mpact of EAFT on 28-day survival: crude and stratified analysis

	N of enrolled patients (EAFT/ non EAFT)	OR	CI 95%	P
Crude analysis	125/122	0.94	[0.77; 1.15]	0.34
Stratified analysis on APACHE II score:				
APACHE II score ≤ 16:	49/50	0.68	[0.53; 0.87]	**0.002**
APACHE II score > 16:	76/72	0.78	[0.55; 1.12]	0.11
Stratified analysis on candida score:				
Candida score ≤ 3 :	28/46	0.86	[0.5; 1.47]	0.32
Candida score > 3:	97/76	0.88	[0.7; 1.11]	0.18
Stratified analysis on Mechanical ventilation:				
unventilated patients:	30/26	0.93	[0.74; 1.18]	0.48
ventilated patients:	95/96	0.94	[0.67; 1.32]	0.35
Stratified analysis on catheterization:				
non-CVC :	12/18	0.53	[0.17; 1.59]	0.23
CVC:	113/104	0.75	[0.7; 1.09]	0.14
Total of stratified analysis (Mantel-Haenszel method)		0.54	[0.7; 1.95]	0.63

EAFT: empiric anti-fungal therapy, OR: odds ratio, CI95%: confidence interval at 95%, APACHE II: Acute Physiology and Chronic Health Evaluation II, CVC: central venous catheter

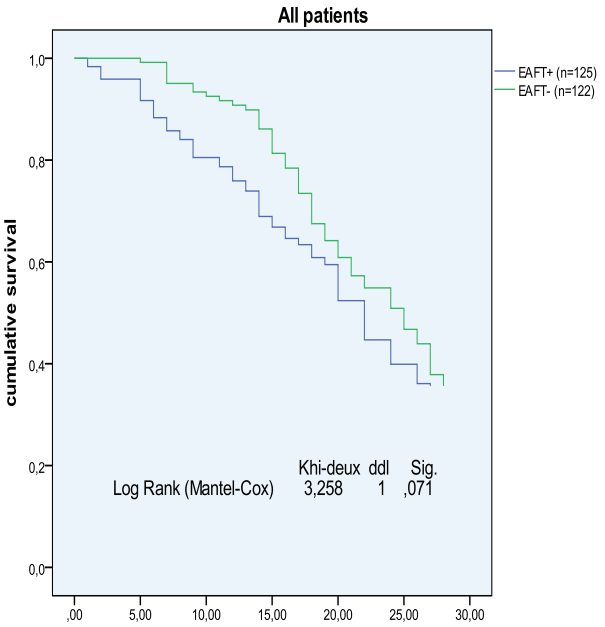


Figure 2. Survival Analysis at 28 days of the study groups

Legend: The mortality in the EAFT group (n=125) was 36% and that of non EAFT group (n=122) was 40.2% without significant difference (p = 0.51). Survival times were comparable to 28 days with median survival time of 25 days versus 22 days in EAFT and non EAFT groups respectively. The survival analysis using the Kaplan-Meier curves tended to significance but without real difference between the two groups (p=0.07). EAFT: empiric anti-fungal therapy

Nevertheless, stratified survival analysis on APACHE II score has regained that EAFT improved survival time for the sub group with APACHE II score lower than 16 : median of 19 days [16-23] versus 15 days [9-17] with p = 0.017 (Figure 3).

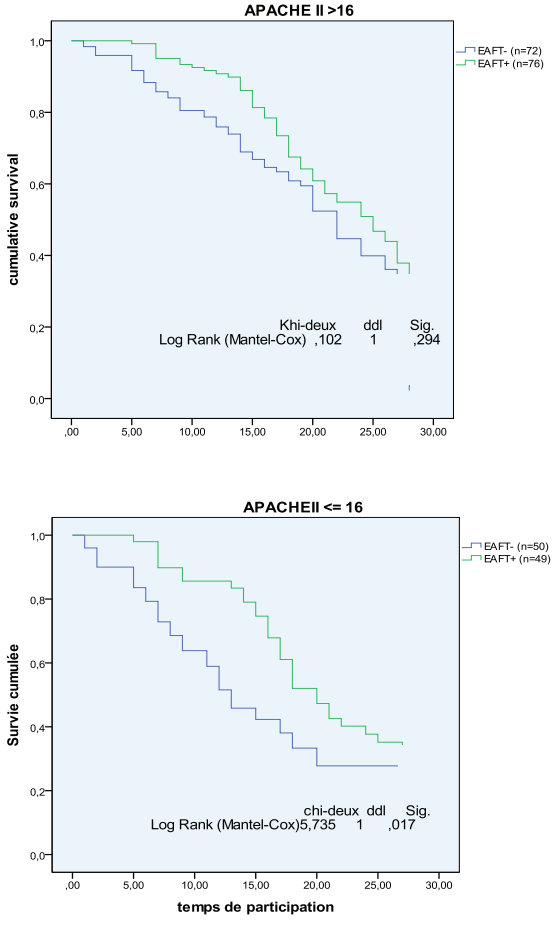


Figure 3. Stratified survival analysis on APACHE II score

Stratified survival analysis on APACHE II score showed that EAFT improved survival for the sub group with APACHE II score lower than 16 (3 A) and no beneficial effect in the subgroup with APACHE II > 16 (3 B).
EAFT: empiric antifungal therapy, APACHE II: Acute Physiology and Chronic Health Evaluation II

EAFT and prevention of new candidemia or *Candida* colonisation:

No difference was shown on the number of new proven candidemia between the two groups [21 (17%) among EAFT group versus 17 (14%) among non EAFT group, p=0.8]. Consequently, the EAFT did not prevent the occurrence of candidemia (OR= 0.96; CI 95% [0.68-2.07], p=0.5). Similarly, the *Candida* colonisation did not differ between our study groups [17 (13.6%) among EAFT group versus 19 (15.5%) among non EAFT group, p=0.88].

Prescription of anti-fungal agents and central venous catheter removal:

The prescribed antifungal in the EAFT+ group were: fluconazole (58%), voriconazole (14.5%), amphotericin B (19.5%) and caspofungin (8%). The EAFT was maintained when the isolated strain was susceptible to the initial antifungal (19/21 candidemia) and changed in the two other cases. Its continuation was discussed case by case in the following situations (catheter-related infection (CRI) without candidemia, candiduria and undocumented infection); and this depending on the underlying diseases and hemodynamic status. It was continued in 27/40 and stopped in 13/40 of cases. Otherwise, empiric antifungal was stopped for a documented bacterial infection in 64 among a total of 125 cases.

Regarding the non EAFT group, the anti-fungal were administered only in case of proven fungal infection [22/122 (18%): 17 cases of candidemia and 5 cases of catheter related infection (CRI); because of the worsening of hemodynamic status. The median delay of antifungal introduction was 4 days after sepsis onset. In this later situation, antifungal therapy was targeted depending on the isolated *Candida* strain and antifungal susceptibility. The most prescribed antifungal was fluconazole since the sensitivity of isolated strains was almost exclusive to fluconazole (18/22: 82%) followed by amphotericin B and caspofungin in 2 cases each.

The central venous catheter was removed routinely in all cases of sepsis.

DISCUSSION

Our study showed that empiric antifungal therapy (EAFT), when administered in patients with late-onset sepsis without documented fungal infection did not improved survival nor prevented candidemia. Nonetheless, a beneficial effect of an EAFT on survival was showed with the subgroup of patients with moderate severity at inclusion (APACHE II score < 16).

The management of invasive candidiasis in critically ill patients is clear when candidemia is confirmed (9). Early treatment and appropriate antifungal in candidemia is related to a better prognosis had shown to reduce mortality in patients with candidemia (7,17,18, 27,28). Preemptive therapy in colonized patients and in those with high-risk of candidemia and unresolved sepsis despite broad broad-spectrum antibacterial therapy remains unclear (29,30). Despite these arguments, the findings of some robust trials (such the INTENSE study: European/American exploratory, multicenter, randomized, double-blind, placebo-controlled trial) were enables to provide evidence that pre-emptive administration of an echinocandin was effective in preventing IC in high-risk surgical ICU patients with intra-abdominal infections (31). Indeed, in that study, the IC incidence was 8.9% and 11.1% for placebo and micafungin arms respectively with a difference at 2.24% [95% CI, (-5.52-10.20)]. Our results were in accordance with these findings concerning the failure of pre-emptive antifungal therapy in preventing candidemia.

Accordingly, clinicians should continue to use predictive scores to identify critically patients who are susceptible to benefit from empirical antifungal treatment. Although it is recognized as a strong risk factor, the candida colonization, which may occur early after ICU admission, does not justify the start of empirical antifungal treatment (32). In our series, adjusted analysis on candida score (<3 vs > 3) didn't show a significant benefit on survival. It is therefore suggested to revise the interest of Candida score among the medical patients. Also, invasive ventilation and central venous catheterization, commonly known as a major risk factors for candidemia (3,33), have not changed the impact of an EAFT on 28-day survival.

Overall, our results were similar to those of a multicenter French study (5 ICUs included in the French Outcome Rea group and 1491 patients) (34) in non-neutropenic, non-transplanted ICU patients. In the AmarCand study that described the management of IC in French ICUs, despite the clinical enhancing after empiric antifungal in 70% among cases of suspected IC, mortality rate remains high and similar in the proven IC group (31.6% vs 34.4%, p=0.42) (25).

Likewise, the EMPIRICUS clinical Trial of Timsit JF et al (21) that was designed to evaluate benefits of early introduction of micafungin in critically ill patients with ICU

acquired severe sepsis and *Candida* colonization failed to conclude in a real survival improvement of such therapy. Indeed, 68% patients in the micafungin group vs 60.2% in the placebo group were alive and free from invasive fungal infection at day 28 (HR=1.35 [95%CI,0.87-2.08]. Nevertheless, the results regarding various predefined subgroups were in favour of micafungin group for patients with [1-3]-β-D-glucan levels >80 pg/mL, [1-3]-β-D-glucan levels of 250 pg/mL, Candida scores at ≥3, and colonization index ≥ 50% (21). Similarly, no significant difference was observed between the 2 groups for the secondary endpoints (day-28 and 90 survivals, the number of organ failure–free days, the rate of ventilator-acquired pneumonia and the serum B-D glucan serum titers evolution) (21). But another interesting and different result emerges from this study: the use of empirical micafungin decreased the rate of new invasive fungal infection in 3% among the micafungin group vs 12% among the placebo group (p=0.008) (21). Our result on this endpoint was not concordant. Indeed, we observed a rate of candidemia in 17% among EAFT group versus 14% among non EAFT group (p=0.8).

In our series the benefit of EAFT on survival improvement was found in the subgroup of patients with moderate severity: APACHE II score <16 (OR= 0.68, CI 95% [0.53-0.87], p=0.002). But, the signification of such result is debatable and requires to be consolidated by further studies with larger series. Probably, the response to an EAFT when it is early introduced in moderately severe patients without multiple organ failures or underlying diseases is more favourable and consequently the gain on survival is greater.

Furthermore, in the latest systematic review on the untargeted antifungal, there was moderate grade evidence that untargeted antifungal treatment did not significantly reduce or increase total mortality (RR=0.93, 95% CI: 0.79 -1.09, p=0.36; participants = 2374; studies = 19). With regard to the outcome of proven invasive fungal infection, there was low grade evidence that untargeted antifungal treatment significantly reduced the risk (RR=0.57, 95% CI: 0.39-0.83, p=0.0001; participants = 2024; studies = 17). The only probable benefit was the reduction of fungal colonization risk (RR=0.71, 95% CI: 0.52-0.97, p= 0.03; participants = 1030; studies = 12) but the quality of evidence was low (35).

In addition to the uncertain improvement of survival by the introduction of an EAFT, it was reported that excessive use of antifungal contributes to the emergence of less sensitive *Candida* species to antifungal agents and Higher minimal inhibition concentration (MIC) for sensitive Candida species (17). Previous use of azoles and candines increase the risk of fungemia to species with higher antifungal MICs. E. Azoulay (18) described a significant relationship between antifungal consumption and probability of being colonized by yeasts with higher antifungal MICs. in ICU patients.

Our findings support the hypothesis that early empiric antifungal therapy did not improve survival and did not prevent a new episode of candiemia. This should lead to a rationalization of the antifungal use among non-neutropenic critically ill patients with ICU-acquired sepsis. The weakness of our study was the retrospective and monocenter design and the nature of the used antifungal (fluconazole). While echinocandins are recommended as first line antifungal therapy, the most common agents used were fluconazole and amphotericin B which remain the two most prescribed agents in underdeveloped countries.

CONCLUSION

No benefits were found of empirical antifungal therapy both in improving survival at 28 day or in preventing a new candidemia among non-neutropenic critically ill patients with a late-onset sepsis. Nevertheless, a beneficial impact on the survival has been objectified at 28 days, in moderately ill patients (APACHE II < 16). Further studies are necessary to resolve the uncertainties around this question. This should lead to improving diagnostic strategies in order to surmount the diagnostic delay of fungal infections and excessive administrations of antifungals without a real benefit.

Declarations of interest: none

Ethics statement: This study was approved by our local institutional review boards, and written patient consent was not required because of the retrospective nature of this study.

Funding sources*:* This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Bitar D, Lortholary O, Dromer F, Coignard B, Che D. Mycoses invasives en France métropolitaine, PMSI 2001-2010: incidence, létalité et tendances. Bull Epidemiol Hebd 2013;12-13:109-14.
2. Zilberberg MD, Shorr AF, Kollef MH. Secular trends in candidemia-related hospitalization in the United States, 2000-2005. Infect Control Hosp Epidemiol 2008;29:978-80.
3. Leroy O, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, et al. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005-2006). Crit Care Med 2009;37:1612-8.
4. Montagna MT, Caggiano G ,Lovero G, De Giglio O, Coretti C, Cuna T, et al. Epidemiology of invasive fungal infections in the intensive care unit: results of a multicenter Italian survey (AURORA Project). Infection 2013;41:645–53.
5. Bassetti M, Merelli M, Righi E, Diaz-Martin A, Rosello EM, Luzzati R, et al. Epidemiology, species distribution, antifungal susceptibility, and outcome of candidemia across five sites in Italy and Spain. J Clin Microbiol 2013;12:4167–72.
6. Lortholary O, Renaudat C, Sitbon K, Madec Y, Denoeud-Ndam L, Wolff M, et al. Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002-2010). Intensive Care Med 2014;40:1303-12.
7. Bassetti M, Righi E, Ansaldi F, Merelli M, Trucchi C, De Pascale G et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med 2014;40:839-45.
8. Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, et al. ESCMID* guidelines for the diagnosis and management of Candida diseases 2012: diagnostic procedures. Clin Microbiol Infect 2012;7:9–18.
9. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012;18:19-37.
10. León C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lerma F, et al. A bedside scoring system («Candida score») for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med 2006;34:730-7.
11. Leroy G, Lambiotte F, Thévenin D, Lemaire C, Parmentier E, Devos P. Evaluation of ''Candida score'' in critically ill patients, a prospective, multicenter, observational, cohort study. Ann Intensive Care 2011;1:50.
12. Eggimann P, Ostrosky-Zeichner L. Early antifungal intervention strategies in ICU patients. Curr Opin Crit Care 2010;16:465–9.
13. Eggimann P, Bille J, Marchetti O. Diagnosis of invasive candidiasis in the ICU. Ann Intensive Care 2011;1:37.
14. Zilberberg MD, Kollef MH, Arnold H, et al. Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study. BMC Infect Dis 2010;10:150.
15. Grim SA, Berger K, Teng C, et al. Timing of susceptibility-based antifungal drug administration in patients with Candida bloodstream infection: correlation with outcomes. J Antimicrob Chemother 2012; 3:707–14.
16. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. Clin Infect Dis 2012;12:1739–46.
17. Fekkar A, Dannaoui E, Meyer I, et al. Emergence of echinocandin-resistant Candida spp. In a hospital setting: a consequence of 10 years of increasing use of antifungal therapy. Eur J Clin Microbiol Dis 2014; 33:1489-96.
18. Azoulay E, Dupont H, Tabah A, Lortholary O, Stahl JP, Français A, et al. Systemic antifungal therapy in critically ill patients without invasive fungal infection. Crit Care Med 2012;40:813 22.
19. Schuster MG, Edwards JE Jr, Sobel JD, , Darouiche RO, Karchmer AW, Hadley Set al. Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. Ann Intern Med 2008;149:83-90.
20. Ostrosky-Zeichner L, Shoham S, Vazquez J, Reboli A, Betts R, Barron MA, et al. MSG-01: a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high-risk adults in the critical care setting. Clin Infect Dis 2014;58:1219-26.
21. Timsit JF, Azoulay E, Schwebel C, Charles PE, Cornet M, Souweine B, et al. Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis,Candida Colonization, and Multiple Organ Failure: The EMPIRICUS Randomized Clinical Trial. JAMA 2016;316:1555-64.
22. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock 2012. Guidelines Committee including the Pediatric Subgroup. Crit Care Med 2013;41:583.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
24. Garey KW, Rege M, Pai MP, Mingo DE. Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis 2006;43:25-31.
25. Leroy O, Bailly S, Gangneux JP, Mira JP, Devos P, Dupont H, et al. Systemic antifungal therapy for proven or suspected invasive candidiasis: the AmarCAND 2 study. Ann. Intensive Care 2016; 6:2.

26. Timsit JF, Azoulay E, Cornet M, Gangneux JP, Jullien V, Vésin A et al. EMPIRICUS micafungin versus placebo during nosocomial sepsis in Candida multi-colonized ICU patients with multiple organ failures: study protocol for a randomized controlled trial. Trials 2013;21:399.
27. Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis 2005;41:1232-39.
28. DiNubile MJ, Lupinacci RJ, Strohmaier KM, Sable CA, Kartsonis NA. Invasive candidiasis treated in the intensive care unit: observations from a randomized clinical trial. J Crit Care 2000; 22:237-44.
29. Playford EG, Eggimann P, Calandra T. Antifungals in the ICU. Curr Opin Infect Dis 2008;21:610-9.
30. Senn L, Eggimann P, Ksontini R, et al. Caspofungin for prevention of intra-abdominal candidiasis in high-risk surgical patients. Intensive Care Med 2009;35:903-8.
31. Knitsch W, Vincent JL, Utzolino S, François B, Dinya T, Dimopoulos G, et al. A randomized, placebo-controlled trial of pre-emptive antifungal therapy for the prevention of invasive candidiasis following gastrointestinal surgery for intra-abdominal infections. Clin Infect Dis 2015;61:1671-8.
32. Eggimann P, Calandra T, Fluckiger U, Bille J, Garbino J, Glauser MP, et al. Invasive candidiasis: comparison of management choices by infectious disease and critical care specialists. Intensive Care Med 2005;31:1514-21.
33. Bassetti M, Trecarichi EM, Righi E, Sanguinetti M, Bisio F, Posteraro B, et al. Incidence, risk factors, and predictors of outcome of candidemia. Diagn Microbiol Infect Dis 2007;3:325–31.
34. Bailly S, Bouadhma L, Azoulay E, Orgeas MG, Adrie C, Souweine B, et al. Failure of Empirical Systemic Antifungal Therapy in Mechanically Ventilated Critically Ill Patients. Am J Respir Crit Care Med 2015;191:1139-46.
35. Cortegiani A, Russotto V, Maggiore A, Attanasio M, Naro AR, Raineri SM, et al. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. Cochrane Database of Systematic Reviews 2016; DOI: 10.1002/14651858.CD004920.