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Impact of echinocandin on prognosis of proven invasive candidiasis in ICU: A post-hoc causal inference model using the AmarCAND2 study

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Summary *Objective:* guidelines recommend first-line systemic antifungal therapy (SAT) with echinocandins in invasive candidiasis (IC), especially in critically ill patients. This study aimed at assessing the impact of echinocandins compared to azoles as initial SAT on the 28-day prognosis in adult ICU patients.
Methods: From the prospective multicenter AmarCAND2 cohort (835 patients), we selected those with documented IC and treated with echinocandins (ECH) or azoles (AZO). The average causal effect of echinocandins on 28-day mortality was assessed using an inverse probability of treatment weight (IPTW) estimator.
Results: 397 patients were selected, treated with echinocandins (242 patients, 61%) or azoles (155 patients, 39%); septic shock: 179 patients (45%). The median SAPSII was higher in the ECH group (48 [35; 62] vs. 43 [31; 58], $p = 0.01$). Crude mortality was 34% (ECH group) vs. 25% (AZO group). After adjustment on baseline confounders, no significant association emerged between initial SAT with echinocandins and 28-day mortality (HR: 0.95; 95% CI: [0.60; 1.49]; $p = 0.82$). However, echinocandin tended to benefit patients with septic shock (HR: 0.46 [0.19; 1.07]; $p = 0.07$).
Conclusion: Patients who received echinocandins were more severely ill. Echinocandin use was associated with a non-significant 7% decrease of 28-day mortality and a trend to a beneficial effect for patient with septic shock.

Introduction

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

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

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

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

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

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

Material and method

Study design

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