

O232

Oral Session

Clinical mycology update 2014

**IMPACT OF EARLY ANTIFUNGAL TREATMENT ON INVASIVE-CANDIDIASIS-FREE SURVIVAL IN ICU PATIENTS VENTILATED FOR MORE THAN 4 DAYS. A PSEUDO-RANDOMIZED TRIAL BASED ON MARGINAL STRUCTURAL MODELS.**

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Objective: Antifungal treatment (AFT) is more effective when administered early in patients with a proven fungal infection. Diagnostic of fungal infection is difficult, since blood cultures are not accurate and often delayed. Probabilist treatment without proven invasive candidiasis (IC) is 75% of treatment started in Intensive Care Unit (ICU). On a cross sectional study we previously showed that more than 5% of ICU patients are treated with AFT without proven invasive candidiasis (Azoulay et al CCM 2012). Impact of AFT on suspected (not proven) IC is suggested but not confirmed by randomized trial. The aim of this study is to estimate the impact of AFT on 30-day survival without IC of ICU patients with suspected IC taking into account baseline and time dependant probability of being treated.

Methods: On the prospectively recorded data from the French Outcomerea group, we selected 5 ICUs for which data about candida colonization and infections were available. We selected patients with at least five day of invasive mechanical ventilation and without proven fungal infection at day five. Patients with neutropenia, organ and bone marrow transplants were excluded. Propensity to receive an AFT each day was assessed using a pooled logistic regression model taking account to patient' severity, case-mix, invasive process, fungal colonization, and the known risk factors of IC. Using Inverse Probability of Treatment Weight method (IPTW), we created, each day, pseudo populations with the same probability of being treated who received AFT or not. A marginal structural Cox model using IPTW estimators was then used to assess the impact of AFT in decreasing the invasive candidiasis free survival. Data were censored at day 30.

Results: We included 2395 (64% men) patients aged  $64 \pm 15$  years. The SAPS II at admission was  $49 \pm 17$ . Type of admission was elective surgery for 12% and emergency surgery for 18% of the patients. Eight percent of the patients were immunosuppressed, 15% had a cancer and 63% had at least one chronic disease. One third (769 patients) were in septic shock or multiple organ failure. AFT was administered to 331 patients (14%) without proven IC during the follow up. Before day 30, death of proven IC occurred in 626 (26%) patients and 18 (0.7%) cases, respectively. After adjustment on baseline and time dependent confounders, empirical AFT initiation was not associated with survival without IC (adjusted Hazard ratio 0.95 (CI95%: 0.65 ; 1.38))

Conclusion: After adjustment of daily probability of receiving AFT and severity, AFT was not associated with invasive candidiasis free survival in ICU patients ventilated for more than 4 days. A sensitivity analysis on predefined subgroups of patients is ongoing. Unmeasured confounders may explain this result and justify further randomized controlled trial.