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The diagnostic accuracy of β -D-glucan, Mannan antigenemia and procalcitonin in unstable critically ill patients with suspected invasive candidiasis

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Background: Empirical antifungal therapy in patients with suspected invasive candidiasis (IC) is desirable in the ICU, but should be balanced with the risk of drug overuse. Targeting the right patients could be improved thanks to clinical rules implementation and biomarkers measurements. Actually, elevated concentrations of β -D-glucan (BDG), Mannan (Mn) antigen and low procalcitonin (PCT) values are associated with the risk of IC in septic patients. However, published data are spared in this setting.

Material/methods: prospective cohort study in a medical ICU (cohort 1: January 2008 to August 2011; cohort 2: June 2015 to November 2016). All of the patients with suspected IC were eligible. Those with the highest expected theoretical risk of IC according to predefined criteria (i.e., uncontrolled sepsis despite broad spectrum antibiotics without any bacterial proven infection, *Candida* score ≥ 3 points, multifocal *Candida* sp. colonization) were included and received empirical therapy with echinocandins, in accordance with ESCMID guidelines. Proven IC was considered whenever blood culture or normally sterile fluid (except urine and broncho-alveolar lavage fluid) was positive for *Candida* sp. Step-down therapy and total duration was let to the discretion of the physician in charge. Procalcitonin and BDG were prospectively assessed at D1, D3, D5, D7 and D10 in cohort 2 patients. Mannan and anti-Mannan antibodies measurements were performed at D1, D5 and D10. Sensitivity (Se), specificity (Sp) were calculated using the optimal cut-off values according to the Youden index calculation.

Results: IC was suspected in 186 patients among who 79 met inclusion criteria (cohort 1: n=39; cohort 2: n=40). IC was proven in 15 (19%) while none of the excluded ones developed IC. In an attempt to refine patients' selection for empirical antifungal therapy when IC was clinically suspected, biomarkers were retrospectively tested at different time-points in cohort 2. The best diagnostic accuracy at D1 was achieved with PCT (Se = 61.3%, Sp = 83.3%), BDG (Se = 48.5%, Sp = 83.3%), and Mn (Se = 41.2%, Sp = 83.3%). Enhanced accuracy was obtained with further measurements of BDG (Se = 85.7%, Sp = 80.0%) and PCT (Se = 80.0%, Sp = 83.3%) at D3, and Mn (Se = 52%, Sp = 100%) at D5. Two consecutive positive BDG at D1 and D3 yielded 86.2 and 60.0% of Se and Sp, respectively. No improvement was obtained with biomarkers combination.

Conclusions: Our clinical rule likely to select among the patients with suspected IC those who could benefit from empirical therapy yielded a high rate of false positive results. Elevated fungal biomarkers such as BDG and Mn, as well as a low PCT could improve its accuracy. Clinical trials are mandatory to evaluate to which extent such a strategy could allow antifungals safe sparing in the ICU.