Editorial

What is the role of empirical treatment for suspected invasive candidiasis in non-neutropenic non transplanted patients in the intensive care unit?—Empiricus strikes back!

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In its last guidelines, published in the early 2016, the Infectious Diseases Society of America (IDSA), sought to answer that difficult question relative to intensive care unit (ICU) patients (1) and stated that: (I) empirical antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from non-sterile sites; (II) empirical antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock; (III) in such a situation, an echinocandin should be the preferred treatment. For these three items, and despite moderate quality of evidence, the strength of the recommendations was strong.

The first question is: 'where do these recommendations come from?'

Even uneasy to be definitely demonstrated, in ICU patients developing invasive candidiasis, a disease associated with a poor prognosis, delaying antifungal administration negatively impacts the outcome, as reported in several studies (2-4). Thus, it is strongly advised to treat as soon as possible, when the diagnosis of proven infection is obtained (usually on blood cultures).

Can we treat before the infection develops? A broad literature has attempted to assess the continuum between Candida colonization and invasive candidiasis (5,6). First, Pittet demonstrated, in a cohort of medico-surgical ICU patients, that the colonization index was a reliable tool to predict the development of invasive candidiasis (7). Accordingly, a high Candida colonization index (usually evaluated once to twice a week) has been proposed to trigger the initiation of systemic antifungal therapy. This approach of treating colonized, but not necessarily infected patients, is called the pre-emptive strategy (8). It has shown promising results: it may lower the rate of invasive candidiasis without affecting Candida species distribution (9). Nevertheless, as Candida colonization is a common event in ICU patients, this strategy implies a heavy burden of unnecessary treatments. Indeed, Piarroux *et al*. reported

that 114 patients had to be treated to avoid 10 invasive candidiasis (out of which only 6 cases of candidemia) (9). Focusing on patients with high-risk of invasive candidiasis could then be a valuable option. However, in a recent study by Ostrosky-Zeichner *et al*., the prophylactic strategy using caspofungin for highest-risk patients also failed to demonstrate an impact on any of the following outcomes: incidence of invasive candidiasis, mortality, antifungal use or ICU length of stay (10). Of note, in this study, a fungal infection biomarker, serum 1,3-β-D-glucan, was not useful to anticipate the diagnosis of invasive candidiasis.

Between treating as soon as the invasive candidiasis has been proven and treating before the occurrence of the infection (prophylactic or even pre-emptive strategy), there is a more challenging situation: the suspicion of ongoing invasive candidiasis which may prompt empirical antifungal therapy. In a study by Schuster *et al*., 270 ICU patients with (I) fever despite broad-spectrum antibiotics, (II) a central venous line, and (III) an APACHE II score higher than 16, were randomly assigned to receive either IV fluconazole or placebo for 2 weeks and were then followed for 4 additional weeks (11). However, this study failed to demonstrate any impact of empirical therapy on the outcome (although fewer invasive candidiasis were observed than expected).

The second question is: 'are these recommendations used/followed in the ICU real life?'

In the observational study by Azoulay *et al*., systemic antifungal therapy was used in 7.5% of ICU patients (12) but two-thirds of these patients had no documented invasive fungal infection. *Candida* colonization and unresolved sepsis (documented or not), were independent predictors of systemic antifungal therapy prescription.

Importantly, some studies reported a relationship between the use of systemic antifungal therapy and the emergence of antifungal resistance in *Candida* strains (13,14). Finally, a recently published cohort of ICU patients also failed to demonstrate the benefits of systemic antifungal therapy on mortality or on occurrence of invasive candidiasis (15). Taken together, all these data therefore question the real value of empirical antifungal therapy in ICU patients without documented infection.

In this context, the results of the Empiricus study were highly expected. The aim of this multicenter double-blind placebo-controlled trial was to determine whether empirical micafungin reduces invasive fungal infection—free survival at day 28 (16).

Two hundred sixty non-neutropenic non-transplant recipient ICU patients were recruited from 19 French ICUs. All had been exposed to broad-spectrum antibiotics and were colonized with *Candida*. To be included, they had to present a severe ICU-acquired sepsis. Importantly, systemic antifungal therapy demonstrated no impact on invasive fungal infection-free survival at day 28. Incidence of invasive fungal infections was relatively low in this very high risk population for invasive candidiasis, being less than 5% (only 12 out of 260 patients). During follow-up, there were significantly more patients with at least one (new) invasive fungal infection in the placebo group than in the micafungin group (15 *vs*. 4; $P<0.01$) but no benefit on mortality was observed. Basically, 119 patients had to be treated to avoid 11 invasive fungal infections. This trial was also relevant because it sought to determine which patients would benefit from empirical systemic antifungal therapy. However, neither clinical criteria (medical versus surgical patients) nor microbiological criteria (colonization index) nor the *Candida* score allowed determining which patients would benefit from antifungal therapy. It is noteworthy that one quarter of the patients were surgical, mainly cardiac surgery, and only few patients suffered from intra-abdominal infection, i.e., an infection site often involving *Candida*. In addition, serum β-D-glucan levels were determined in all patients at baseline and during follow-up. Unexpectedly, baseline β-D-glucan failed in identifying patients likely to benefit from antifungal therapy. As its level was not influenced by antifungal therapy during the subsequent days, β-D-glucan was also of little help to guide de-escalation of anti-fungal therapy.

To summarize, 'are there any unresolved questions?'

The study by Timsit *et al*. improves our understanding of fungal infections and their treatment in the ICU. Nevertheless, several questions may warrant further investigations. (I) Gastrointestinal surgical patients and/or those admitted for necrotizing pancreatitis may constitute a higher risk group that was under-represented in that study (17,18); (II) the study excluded immuno-compromised patients including solid organ transplant or hematopoietic stem cell recipients, which is logical regarding the specificities of fungal infections among that population (19). These immuno-compromised patients are frequently hospitalized in the ICU and represent a challenge for both

diagnosis and treatment of fungal infections (20-22); (III) the lack of use of selective digestive decontamination in the French ICUs may have been balanced with prior exposure to broad spectrum antibiotic therapy. However, it could also explain an incidence of invasive fungal infection lower than that observed in other countries (23); (IV) besides β-D-glucan, the evaluation or the discovery of other biomarkers is warranted to determine, more precisely, which patients would benefit from systemic antifungal therapy to prevent invasive candidiasis, a still unresolved issue (24).

As a conclusion, the Empiricus study demonstrates that non-neutropenic non-transplant recipients ICU patients with sepsis should not be systematically treated empirically for invasive candidiasis, even when they present risk factors. This important message will strengthen a better use of systemic antifungal therapy and antifungal stewardship that is warranted for both preventing selective pressure and economic purposes (25,26). Indeed, it is certainly relevant to have the same fears with respect to antifungals use that with respect to antibiotics (27,28). Limiting wide use would limit the emergence of resistant strains (29).

It is likely that these findings may encourage the revision of the international guidelines.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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