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Empiric/pre-emptive anti-Candida therapy in non-neutropenic ICU patients

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Abstract

The potential of the systemic antifungal treatment of non-immunocompromised patients with sepsis, extra-digestive *Candida* colonization and multiple organ failure is unknown, although it represents three out of four antifungal treatments prescribed in intensive care units. It may allow an early treatment of invasive fungal infection at incubation phase, but exposes patients to unnecessary antifungal treatments with subsequent costs and antifungal selection pressure. As early diagnostic tests for invasive candidiasis are still considered insufficient, the potential of this strategy needs to be demonstrated by a randomized controlled trial. Such a trial is currently ongoing.

Candidiasis is a mortality risk factor

Candida is one of the most frequently recovered pathogens in patients with hospital acquired bloodstream infections [1–3], where it is associated with a mortality rate from 30 to more than 60% in case of septic shock [4–8].

Major risk factors for *Candida* colonization include length of intensive care unit (ICU) stay, use of parenteral nutrition, broad-spectrum and long-term antibiotics, central lines, and abdominal surgery. Importantly, a continuum exists between *Candida* colonization and candidemia [9–11]. Thus, a colonization index (number of colonized sites/number of sampled sites) of >0.5, with recovery of the same *Candida* species or genotypes in the colonized sites and bloodstream, has been set up and is associated with an increased risk of candidemia [11]. Studies conducted to develop a *Candida* score showed that factors associated with candidemia were surgery, multiple-site *Candida* colonization, severe sepsis, and parenteral nutrition [12]. Thus, *Candida* colonization, although not unique, is a reliable independent risk factor for candidemia [13–15]. Therefore, early systemic antifungal therapy (SAT) deserves consideration in ICU patients in whom they are increasingly used [16,17].

The diagnosis of candidemia is often difficult and delayed because the sensitivity of blood culture bottles (even in specific milieu) is not higher than 75% and decreased by previous antifungal therapy [18].

Non culture-based assays have been developed to improve the diagnosis of invasive candidiasis. These new tools have been mainly tested in hematological patients and in surgical ICUs. (1-3)-β-D-glucan is a cell wall component of *Candida* sp. and other fungi. It becomes detectable early during invasive candidiasis but may also rise in other fungal infections. Indeed, (1-3)-β-D-glucan rises in cases of aspergillosis, and *Pneumocystis jirovecii* infections, but also in rare infections, such as infection with *Fusarium* spp., *Acremonium* spp., *Sporothrix schenkii*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Trichosporon* spp. and *Saccharomyces cerevisiae*. Importantly, (1-3)-β-D-glucan is not found in Cryptococcosis or Zygomycetes infections (*Adsidia*, *Mucor*, *Rhizopus*). (1-3)-β-D-glucan remains detectable for more than one month after invasive candidiasis [19,20]. The cut off value proposed for hematological patients is 80 pg/ml but it appears to be higher in ICU patients [20,21].

False positive results have been reported in cases of dialysis with cellulose membrane, albumin perfusions, intravenous immunoglobulin administration, antibiotic therapy with coamoxiclav or Piperacillin-Tazobactam, and bacteremia [21]. The reported sensitivity and specificity of (1-3)-β-D-glucan is 57–97% and 56–93%, respectively. Given the low prevalence of invasive candidiasis in non-neutropenic patients, a negative test is adequate to rule out a diagnosis of infection [22]. In the recent study of the FUNGINOS group [23], in a selected population of surgical ICU patients, two consecutive measurements of (1-3)-β-D-glucan of more than 80 pg/ml were associated with a reasonable diagnostic value (positive predictive value of 72%, negative predictive value of 80%) that need to be confirmed in further study on other non-surgical ICU populations. Importantly, (1-3)-β-D-glucan positivity preceded the diagnosis of invasive candidiasis by 5 days in mean.

Mannan, a polysaccharidic antigen from *Candida* cell wall, is another potential diagnostic test. Both mannan antigen and anti-mannan antibodies could be measured using one enzyme-linked immunosorbent assay (ELISA) kit. Mannanemia is more specific than (1-3)-β-D-glucan but showed a lack of sensitivity in a recent study on candidemia [20]. The combination of both tests possesses an acceptable diagnostic value (86% specificity and 83% sensitivity) in a recent meta-analysis [24].

Finally, detection of *Candida* DNA using polymerase chain reaction (PCR) seems to be both sensitive and specific in the available literature but standardization of tests is lacking [25].

Early treatment of candidemia decreases mortality of ICU patients with septic shock

Delays in initiating appropriate treatment have been associated with increased mortality in patients with bloodstream infections [4,26]. Similar findings have been reported in patients with candidemia [26–29]. This is especially the case for critically ill patients with septic shock [8]. Importantly, the control of the infected source acts in synergy with the antifungal therapy. In a recent study, both a delay in antifungal treatment of more than 24 hours (odds ratio=5.99, P=0.048) and the absence of source control within the first 48 hours (odds ratio=2.99, P=0.001) were associated with the risk of death in the case of septic shock due to candidemia [7].

Overuse of antifungals modifies fungal ecosystem and promotes antifungal resistance

The usual risk factors described in the more recent predictive scores included variables that are frequent, and lead us to treat 10–20% of the ICU patients [13,30]. More than two-thirds of these treatments are given without definitive proof of invasive fungal infections [30].

As an example, the colonization index's positive predictive value is less than 9% in the EPCAN study [14]. In medical ICU patients, 39% developed a colonization index of more than 0.5, while, in the same period, no invasive fungal infections were diagnosed [10].

New antifungal agents are well tolerated and over-treatment might be considered safe on an individual basis. However, new data from the US and Europe clearly demonstrate that the overuse of antifungal drugs contributes to both the emergence of *Candida* species that are known to be less sensitive to antifungal agents, as well as to the increased occurrence of sensitive *Candida* species with increased minimum inhibitory concentrations (MICs). Recently, Lortholary *et al*. reported that azole derivatives and candins pre-exposure increased the risk of fungemia due to species with higher MICs to the corresponding antifungal agents [31]. Pfaller *et al*. found an increase in rates of fluconazole-resistant *Candida glabrata* intermediate or resistant to candins over time, from less than 4% between 2000 and 2002 to more than 12% between 2008 and 2010 [32]. Dannaoui *et al*. reported 20 episodes of fungal infections caused by candin-resistant *Candida* spp. that were harboring diverse and new resistance mutations [33]. For 12 patients, the initial isolates (low MICs, wild-type FKS gene) and the subsequent isolates (after caspofungin treatment, high MICs, FKS mutation) were genetically identical [33]. We also recently described a significant relationship between systemic antifungal therapy (SAT) consumption and MICs of colonizing and infecting fungi in ICU patients [34].

Finally, two studies clearly showed that the pre-exposure to candins was associated with episodes of *C. glabrata* septicemia with strains of reduced susceptibility to candins that harbored FKS mutation. Such strains were associated with a higher rate of clinical failure of echinocandin therapy [35,36].

Obviously, SAT should be used applying the same rules as for other antimicrobial agents. It must be effective and safe for the patient himself, and also for future patients.

Empiric/pre-emptive treatment of ICU patients has never proved to be effective

Regarding which benefits to expect from an empirical or pre-emptive SAT in critically ill non-immunocompromized patients, the current literature is inconclusive, and trials demonstrating the efficacy of SAT in

colonized patients with unresolved sepsis and organ dysfunction are warranted.

Empiric therapy is usually defined as a therapy instituted in patients with clinical signs suggestive of ongoing invasive infection (new systemic inflammatory response syndrome, organ failures), while pre-emptive therapy is given to patients with risk factors and one or more positive markers such as a rising colonization index or (1-3)-β-D-glucan elevation above a threshold value that remains to be determined in the ICU setting.

One may question the potential of empirical therapy of ICU patients with sepsis and risk factors of invasive fungal infection, and of pre-emptive therapy of ICU patients with a positive biomarker such as *Candida* colonization or (1-3)-β-D-glucan.

Regarding the so-called empirical therapy, no clear demonstration of efficacy has been published. In a randomized controlled double-blind trial, a high dose of fluconazole failed to reduce survival free of invasive fungal infection in medical-surgical ICU patients with non-resolving sepsis. In this study, *Candida* colonization was diagnosed at inclusion of patients in only a quarter of the cases [37]. The issue remains uncertain because the diagnosis of invasive fungal infection remains a challenge in ICU. In a one-day prevalence study, the authors declared 17% of nosocomial infections to be due to *Candida* spp. [38], but only 99/14,414 patients developed proven candidemia.

Candida colonization is a frequent event in ICU patients [14]. The colonization index, validated 20-years ago in long-term surgical ICU patients, has been broadly challenged. For instance, its positive predictive value is less than 9% in the EPCAN study [14]. Furthermore, in medical ICU patients, 39% developed a colonization index of more than 0.5, while, within the same period, no invasive fungal infections were diagnosed [10]. Colonization index remains an important way to characterize the dynamics of the colonization of ICU patients, which increases early in patients who will go on to develop invasive candidiasis, but its bedside practicality remains limited [39].

One before-and-after study showed decreased ICU-acquired candidemia rate when using a colonization index-based fluconazole therapy, but without any survival benefits [40].

Likewise, we are looking forward to having improved diagnostic strategies to increase the sensitivity, specificity and predictive values of the available tools, as well as to reduce diagnostic delays. New tools such as assays to measure (1-3)-β-D-glucan levels provided promising results in ICU populations [23,41,42]. However, (1-3)-β-D-glucan is not specific to candidiasis, is higher than 80 pg/ml in many ICU patients without invasive candidiasis, and decreases slowly under effective treatment [19,43,44].

Over the last 15 years, several studies have evaluated the potential benefits from SAT in ICU patients overall [45–50], and in the subset of ICU patients with risk factors for candidemia or sepsis of unknown origin [37,40]. Pre-emptive SAT has been suggested for the sickest surgical ICU patients, most notably those with peritonitis [51]. More recently, an exploratory study compared the efficacy and safety of micafungin as a pre-emptive treatment of invasive candidiasis vs. placebo in high risk surgical subjects with intra-abdominal infections in a multicenter randomized control trial (INTENSE NCT NCT01122368). Results are available in clinicaltrials.jp (http://www.clinicaltrials.jp/user/display/file/9463-EC-0002%20synopsis.pdf?fileId=983). A total of 241 patients were analyzed in the full analysis set. In this study, the rate of independent data reviewing board-confirmed invasive fungal infection after inclusion was similar in the micafungin and placebo arms (8.9 vs. 11.1%). There was no difference in mortality, invasive fungal infection-free survival, and improvement of organ failures between the micafungin and placebo arms. Micafungin significantly reduced the colonization index.

In another multicenter, randomized, double-blind, placebo-controlled trial (MSG 01) Ostrosky-Zeichner *et al.* tested the use of caspofungin in 222 adults who were in the ICU for at least 3 days, were ventilated, received antibiotics, had a central line, and had 1 additional risk factor (parenteral nutrition, dialysis, surgery, pancreatitis, systemic steroids, or other immunosuppressive agents) [52]. The primary endpoint was the incidence of proven or probable invasive candidiasis. Unfortunately, in terms of trial protocol, patients with sepsis and with two consecutive (1-3)-β-D-glucan samples above 80 pg/ml were classified as probable cases of invasive candidiasis, which allowed the investigators to break the blind and to administer them pre-emptive therapy with caspofungin. The pre-emptive approach analysis included all patients who received the study drug, including those positive at baseline. The incidence of proven/probable invasive candidiasis in the placebo and caspofungin arms was 30.4% (31/102) and 18.8% (22/117) for the pre-emptive approach (P=0.04). There were no significant differences in the secondary endpoints of mortality, antifungal use, or length of stay.

Both studies give rise to comments. The rate of proven invasive candidiasis was low (6.9% and 11.1% in the

placebo arms of INTENSE and MSG-01 studies); it suggests that the targeted population is not fully understood and leads to suggestions that the studies are considerably underpowered. The decrease in the risk of probable infection in the MSG-01 study was not associated with an improvement of vital status or duration of ICU stay. This may be explained by the fact that (1-3)-β-D-glucan serum level above 80 pg/ml should not be considered an accurate biomarker of invasive candidiasis.

Patients that may possibly benefit from early (empiric or pre-emptive) antifungal treatment are those with a high risk of invasive candidiasis. Given the results of the study from Schuster *et al.* [37] and the work performed by the EPCAN groups [12,53], we postulated that the combination of multiple organ failure, sepsis of unknown origin and multiple colonization with *Candida* in mechanically ventilated patients for more than four days and receiving board spectrum antibacterial agents, should select a population with a particularly high risk of life-threatening invasive candidiasis. The potential benefits ascribable to SAT in this population is currently being tested in the EMPIRICUS trial [54]. Results will be available in early 2015.

Conclusion

We consider that definite rules could not be derived for systemic antifungal therapy. We need to strongly encourage and promote studies able to improve diagnostic strategies, and randomized control trials further defining the efficacy of SAT in colonized patients with sepsis and multiple organ failures.

Pre-emptive treatment should be decided at bedside, after sampling at least two separate blood cultures with 10 ml volume of blood preferably on selective milieu, in view of the uncertainty involved. To contain the antifungal selection pressure that is starting to rise, we also propose considering "stopping rules" after 5 days when no proven invasive candidiasis occurs.

Until the development of accurate early diagnostic tests or the results from ongoing trials are available, a demonstration of a clinical benefit of treatment of such patients is warranted to solve uncertainties in the issue deciding antifungal treatment in ICU setting.

Abbreviations

ICU, intensive care unit; MIC, minimal inhibitory concentration; SAT, systemic antifungal therapy.

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Jean-François Timsit's university received research grants from Astellas and Merck. Jean-François Timsit received educational grants from Gilead and lectured in symposia organized by Astellas, Pfizer and Merck. Sébastien Bailly and Sarah Chemam declare that they have no disclosures.

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