Main topic of this debate will be "untargeted antifungal treatment".

Should we start antifungal treatment before the IFI diagnosis? If yes, which criteria?

Are there indeed any criteria for starting empirical antifungal treatment in icu patients?

What has the experience in the antifungal treatment has shown us? any change of the paradigmas?

Another question may be: "which antifungal"? (there is a -almost commercial-competition).

What is the duration of antifungal treatment?

What is the role of these issues on morbidity, mortality and cost?

Nahit Çakar
Associate Editor

Should we Administer Antifungal Drugs Before the Diagnosis of Invasive Fungal Infection in Non-Neutropenic Critically Ill Patients?

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Invasive fungal infections (IFI) are a major cause of morbidity and mortality in critically ill patients. Candida spp. infections are the most frequent fungal infections in the Intensive Care Unit (ICU), ranking the third most common isolated pathogen and the fourth most common cause of nosocomial bloodstream infection (1-3). Attributable mortality due to Candida spp. infections ranges from about 42 to 63% (4, 5). Several observational studies described a strict correlation between an early adequate antifungal treatment and reduced mortality in critically ill patients with fungal infections (6, 7). However, the definitive diagnosis of fungal infections, based on microbiological identifications, requires several days and usually occurs late in the clinical course (8).

For nearly 30 years, clinicians and researchers have tried to prevent and treat early IFI in critically ill patients (9). Three antifungal strategies have been used in clinical practice for these purposes: 1) 'prophylaxis' defined as the administration of antifungal agents in patients without proven or suspected fungal infections but with risk factors for its development (e.g. fungal colonization, central venous catheter, parenteral nutrition, dialysis, abdominal surgery, broad spectrum antibiotics); 2) 'empiric treatment' defined as antifungals administration triggered by signs and symptoms of infection in patients at risk for IFI; 3) 'pre-emptive treatment' defined as treatment triggered by microbiological evidence of fungal infection, without definitive microbiological identification (e.g. positive biomarkers such as 1-3-beta-D-glucan, mannan-antimannan antibodies, procalcitonin); (10, 11). The common point of these strategies is that they are 'untargeted treatments' since they are not driven by an established diagnosis of IFI. In clinical practice, it is not always easy to clearly differentiate these strategies, which are used in patients with a different grade of probability of fungal infection.

The number of patients potentially treated with antifungals without IFI diagnosis is high. In a 1-day cross-sectional multicentre cohort study, Azoulay et al. demonstrated that 7.5% of patients admitted to 129 participating ICU were receiving systemic antifungal drugs. Two-third of these patients had no documented invasive fungal infection (12).

First randomized controlled trials (RCTs) globally showed a reduction in the incidence of IFI and mortality with the administration of azoles in both sur-

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gical and medical critically ill patients (13) and contributed to the widespread use of not-targeted antifungal approaches. However, subsequent large multicentre RCTs did not confirm these results. Schuster et al. (14) randomized 270 critically ill patients with fever despite administration of broad-spectrum antibiotics to fluconazole or placebo and did not find any difference in terms of mortality or incidence of IFI. Ostrosky-Zeichner et al. (15) randomly assigned 222 patients with at least 3 days of ICU stay and risk factors for fungal infections to receive caspofungin or placebo. The incidence of proven/probable IFI and mortality were not significantly different between the two groups. In another multicenter RCT, Knitsch et al. (16) enrolled 252 critically ill patients with localized/generalized intra-abdominal infection either of community or of nosocomial origin requiring emergency surgery. They were randomized to receive micafungin or placebo. The study was unable to provide any significant difference in terms of invasive candidiasis or mortality between groups.

Recently, a Cochrane systematic review investigated the effect of prophylaxis, pre-emptive and empiric antifungal treatment with any antifungal drug (untargeted antifungal treatment) in non-neutropenic critically ill patients (9). The review included 22 RCTs and 2761 patients. There was moderate quality of evidence that untargeted antifungal treatment did not significantly reduce mortality (RR 0.93, 95% CI 0.79 – 1.09), whereas the risk of IFI was significantly reduced by about 45% with low quality of evidence (RR 0.57, 95% CI 0.39 – 0.83). Most of the included trials investigated prophylaxis or empiric treatment. In subgroup analysis, neither prophylaxis nor empiric treatment was associated with significant mortality reduction (17). Very recently, another multicenter RCT confirmed these results. In the EMPIRICUS trial, Timsit et al. (18) enrolled 260 non-neutropenic critically ill patients with ICU-acquired sepsis, multiple Candida colonization, multiple organ failure, exposed to broad-spectrum antibiotics. Patients were randomized to receive empirical antifungal treatment with micafungin or placebo. The primary outcome was survival without proven IFI at 28 days after randomization and it was not significantly different between the two groups. Interestingly, the use of empirical micafungin reduced the incidence of IFI compared to placebo.

The most recent clinical practice guideline for the management of candidiasis by the Infection Disease Society of America (IDSA) stated that empiric antifungal treatment with an echinocandin should be considered in critically ill patients with risk factors and no other cause of fever, whereas it should be started as soon as possible in patients with risk factors and septic shock (19). Notably, a 'strong recommendation' and moderate quality evidence supports these statement. Regarding intra-abdominal candidiasis, IDSA recommendation underlined that empiric treatment should be considered in patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, such as recent abdominal surgery, anastomotic leakage or necrotizing pancreatitis (strong recommendation; moderate-quality evidence). It should be underlined that IDSA did not take into account, for timing reason, the evidence from most recent RCTs and Cochrane review.

From available evidence, a paradox arises: the use of antifungal drugs before definitive diagnosis of infection in non-neutropenic critically ill patients is able to reduce the incidence of IFI without any mortality benefit (20). This should bring us to rethink the pathophysiology of fungal infections in ICU patients and to consider other forms of antifungal strategies for future trials (21). On clinical grounds, a widespread use of untargeted antifungal treatment is no longer justified. A case-by-case decision based on grade of probability of the infection, risk factors, available biomarkers and balancing potential benefit with costs and risk of increasing resistance may be the most reasonable answer to the title question.

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