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WHAT'S NEW IN INTENSIVE CARE

Antifungal stewardship in critically ill patients

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In critically ill patients, empirical antifungal treatment is commonly used because of poor prognosis of these infections, especially when initial antifungal treatment is inappropriate or delayed. In addition, accuracy of available diagnostic tools is limited. However, excessive use of antifungals is potentially associated with side-effects, higher cost and emergence of pathogenic fungi. We aim to provide a short summary of recent data on invasive fungal infections management to improve antifungal use in critically ill patients.

Biomarkers

Clinical implementation of currently available fungal-specific biomarkers, for both early diagnostic or rule-out assays, is relevant. 1,3-β-D-glucan (BDG), a cell wall component of many fungi, is the most commonly used diagnostic assay for invasive candidiasis (IC), as a stand-alone test or in combination with other biomarkers (mannan antigen [Mn-Ag], anti-mannan antibody [Mn-Ab] and *Candida albicans* germ tube antibody), not yet suitable as single antifungal stewardship tools [1].

BDG diagnostic performance is superior to bedside clinical prediction models and colonization indexes, showing, in settings at low pre-test probability (IC rate < 5%), both high sensitivity (74–86%) and negative predictive value (> 95%) [2]. Conversely, false positive results have been documented in many circumstances (i.e. heavy mucosal and skin fungal colonization, albumin and immunoglobulin administrations, haemodialysis, packing with surgical gauzes, non-glucan-free laboratory equipment), decreasing the overall specificity (60%) and positive predictive value (< 15%) of the test in patients with low-intermediate IC risk.

Notably, a recent multicentre randomized trial [3], comparing a BDG-driven strategy with standard care (culture-based targeted therapy), was not able to demonstrate any survival benefit from the implementation of two positive BDG results for early IC diagnosis and treatment. Further, in the biomarker-guided arm, antifungal therapy was initiated in almost half of patients despite the low rate of IC (14%). Therefore, in critically ill patients carrying a low risk of IC, a BDG-guided pre-emptive approach cannot be recommended, due to the high probability of antifungal overuse in the absence of Candida infection. Conversely, data from two randomized trials support the use of a biomarkers-driven strategy (using BDG alone or in combination with Mn-Ag/Mn-Ab) as a rule-out diagnostic tool, allowing prompt and safe interruption of antifungals in patients without mycological confirmation of invasive yeast infection [4, 5]. This strategy has been included in current guidelines [1]. Although the use of biomarkers in specific populations is still to be validated, their use is mostly beneficial in patients admitted in intensive care unit (ICU) at high risk for IC.

Galactomannan (GM) is the hallmark biomarker for the diagnosis of invasive pulmonary aspergillosis (IPA) in critically ill patients. This cell wall component may be detected in both serum and bronchoalveolar lavage (BAL), the latter sampling showing higher sensitivity and specificity (≥ 90) at optical density index cut-off ≥ 1, which is higher than the serum one (≥ 0.5) [6]. Severe viral pneumonia (i.e. due to Influenza and SARS-CoV-2) is associated with Aspergillus bronchoalveolar lavage (BAL) identification (hyphae microscopic evidence, BAL culture positivity, serum/BAL GM positivity), frequently reflecting only tracheobronchial colonization [7]. However, although a definite IPA diagnosis always requires clinical, radiological and microbiological

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criteria, such patients are often treated with anti-mould drugs, in absence of true invasive infections, raising many concerns in terms of ecological pressure and potential toxicity. Other risk factors for IPA include immunosuppression, chronic obstructive pulmonary disease, and cirrhosis. Given the clinical utility of Aspergillus biomarkers from BAL and the limited availability of daily GM testing with turn-around time < 24 h, new rapid diagnostic tests were developed. Aspergillus lateral flow assays, although still limited by low specificity, have been recently introduced in the clinical practice, as point-of-care tools for early IPA diagnosis and antifungal therapy optimization [8].

De-escalation

De-escalation of antifungal treatment is defined as either a switch from initial antifungals, except fluconazole, to triazoles, or discontinuation of initial antifungal treatment within the 5 days following their initiation [1]. In a landmark multicenter observational study, Bailly and colleagues [9] reported an incidence of antifungal de-escalation at 22% (142 of the 647 non-neutropenic critically ill patients). Antifungal treatment was stopped in 34% of patients in whom de-escalation occurred. Although de-escalation of antifungal treatment was associated with reduced duration of antifungal treatment, no negative impact of de-escalation was reported on outcomes.

In a single-center retrospective study, Jaffal and colleagues [10] reported a similar incidence of de-escalation of antifungal treatment (20%, 38 of the 190 critically ill patients receiving systemic antifungals). Invasive mechanical ventilation was independently associated with lower rates of de-escalation (OR 0.25 [95% CI 0.08–0.85], $p = 0.013$). Total duration of antifungal treatment was significantly shorter in patients in whom de-escalation was implemented. No significant differences were found in the duration of invasive mechanical ventilation, length of ICU stay, ICU mortality, or 1-year mortality between patients with de-escalation and those with no de-escalation. Importantly, these studies were observational and physicians probably deescalated antifungal in patients who were improving. Further randomized controlled trials are necessary to confirm their results.

Modeling provided evidence that when treating patients with invasive candidiasis in patients at risk of azole-resistant infections, de-escalation from micafungin has potential cost savings associated with improved clinical success rates [11]. A recent large observational study reported an early de-escalation rate of 23% in patients with candidemia (54 of 235 patients) [12]. Early de-escalation was more common in catheter-related candidemia, and episodes caused by *Candida parapsilosis*, yet it was less frequent in ICU patients, infections caused by *Nakaseomyces glabrata*, and candidemia from an unknown source. After adjustment for confounders, early de-escalation was not associated with mortality.

Current European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines strongly recommend de-escalation after receiving microbiological results. All available studies, have evaluated de-escalation in patients with suspected IC. To our knowledge, no study has evaluated de-escalation of antifungal treatment in patients with suspected aspergillosis. Further, no study has specifically evaluated de-escalation in immunosuppressed patients.

Other methods to improve antifungal use

In critically ill patient, therapeutic drug monitoring (TDM) was suggested to adjust for variability in antimicrobial pharmacokinetic (PK), related in part to patient covariates (e.g. body weight and renal function), and to unexplained PK variability (i.e. inter-individual, and intra-individual PK variability). TDM-guided dosing has been shown to be clinically beneficial for voriconazole, and was recently recommended in routine in critically ill patients [13].

Candida T2 Magnetic Resonance (T2MR) has recently been in tested in patients with suspected Candida bloodstream infection. Although T2MR is faster than blood cultures, its accuracy in identifying Candida is reported to be moderate [14]. The main limitation of T2MR is that only five *Candida* spp. are included in the panel. In a multicentre study, T2MR identified bloodstream infections that were missed by blood cultures in patients receiving antifungal therapy [15]. Thus, T2MR may improve care by shortening time to Candida detection and species identification compared to blood cultures.

A recent large cohort, compared hospitals with an infectious disease (ID) physician to those with no ID physician on site [16]. The presence of an ID specialist was associated with lower total inpatient antibacterial use and reduce consumption of broad-spectrum antimicrobials. Total antibacterial exposure (inpatient plus post-discharge) was lower among patients at ID versus non-ID sites. To our knowledge, no specific data are available on on-site ID physician and antifungal use, and future studies should evaluate the impact of ID specialist presence and antifungal use.

A systematic review of 13 single-center studies on antifungal stewardship (AFS) programs concluded that AFS interventions can improve performance measures and decrease antifungal consumption, with no negative impact on outcomes [17]. However, several limitations of the included studies preclude definite conclusions.

Finally, fungal colonization is common and positive urine or respiratory specimen for fungi should not be

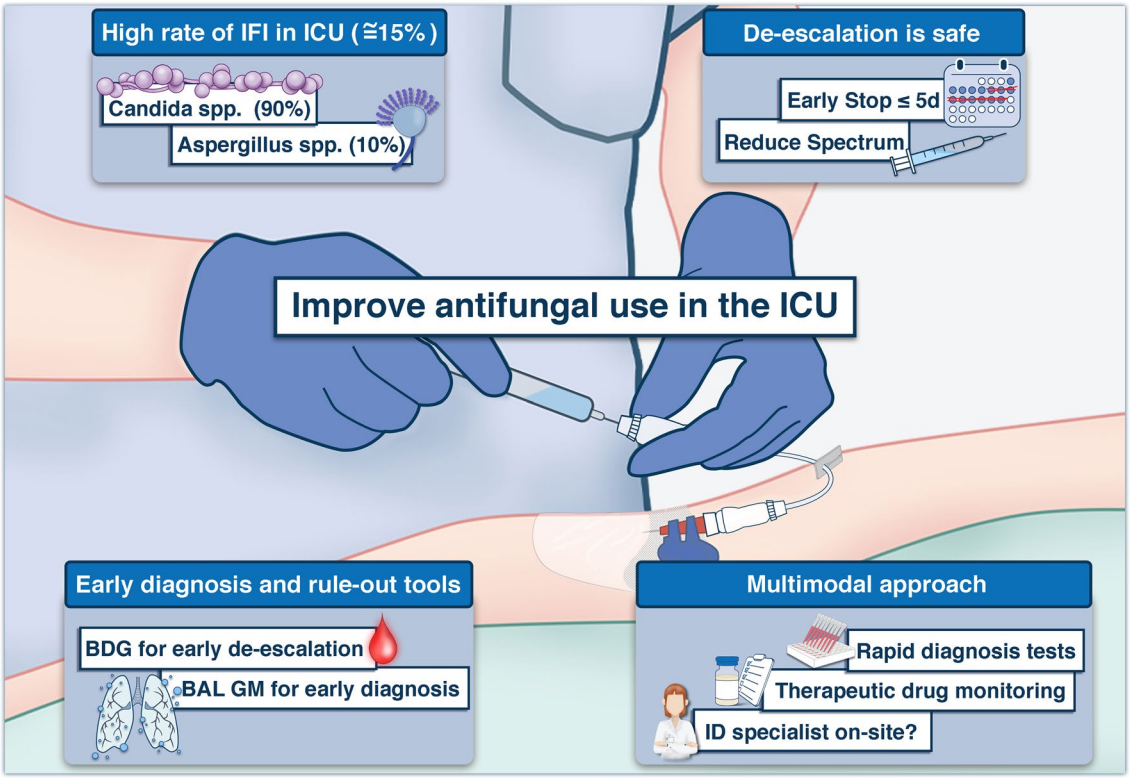

Fig. 1 Antifungal stewardship in critically ill patients. *ICU* intensive care unit; *BDG* 1,3-β-D-glucan; *GM* galactomannan; *ID* infectious disease

treated with antifungals, in absence of signs of systemic IC or IPA.

Take-home messages

AFS can improve performance measures and decrease antifungal consumption, with no negative impact on outcomes. BDG are helpful to stop unnecessary treatment in patients with IC, but should probably not be used to initiate antifungal therapy in patients with low probability of IC. De-escalation of antifungal treatment is safe and should be performed in critically ill patients. Routine TDM is recommended in patients receiving voriconazole. Accuracy of T2M3 in diagnosing IC, and the role of ID physicians in better use of antifungals in the ICU should be further evaluated (Fig. 1).

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Data availability
Not applicable.

Declarations

Conflicts of interest
GDP received fees for lectures from Pfizer, Gilead, Biomérieux. IML fees for lectures from MSD, Gilead, and Mundipharma. SN received fees for lectures from MSD, Pfizer, Gilead, Biomérieux, BioRad, and Fisher and Paykel, and Mundipharma.

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