EDITORIAL

Optimizing the Treatment of Critically Ill Patients Utilizing Beta-D-glucan: The Time is Now

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Invasive candidiasis can result in considerable morbidity and mortality in critically ill patients. A study conducted at 27 Indian intensive care units (ICUs) from April 2011 to September 2012 revealed an incidence of 6.51 cases per 1,000 ICU admissions, with 30-day crude and attributable mortality rates of 44.7% and 19.6%, respectively.[1] Consequently, the concept of prophylactic and empirical use of antifungals in the ICU has gained prominence.

However, randomized controlled trials have not demonstrated a reduction in mortality using prophylactic or empirical antifungal therapy compared to placebo. A Cochrane review on the use of prophylactic antifungal agents in non-neutropenic, critically ill patients concluded that there is moderate-quality evidence that using antifungals before a definitive diagnosis of invasive fungal infection is made is not associated with a significant reduction in mortality.[2]

Beta-D-glucan has a high negative predictive values (NPV), making it useful for the de-escalation of empiric antifungal therapy. Despite discontinuation of antifungal agents in patients with negative beta-D-glucan not being endorsed in treatment guidelines, negative tests do provide useful evidence as part of a broader assessment that could support discontinuation of empirical antifungals.

The NPV of beta-D-glucan varies from 90 to >99% as the prevalence of invasive candidiasis decreases from 30% to 2%, respectively. The positive predictive value is much lower, at <70%.[3] False-positive results in the ICU cohort can be attributed to factors such as surgical gauzes, renal dialysis, intravenous albumin, use of broad-spectrum antibiotics, etc. Therefore, in the ICU, a negative beta-D-glucan test can safely exclude invasive candidiasis if the pre-test probability is low or moderate.

If the test is positive, initiating antifungal therapy is recommended only in patients at high risk of candidiasis, such as those with recurrent gastrointestinal perforation, hepatobiliary anastomotic leakage, necrotizing pancreatitis, or a *Candida* score ≥ 3. Even in this group, two consecutive positive tests are recommended before starting therapy.

Candida colonization index, the Ostrosky-Zeichner clinical prediction rule, and the *Candida* score all have high NPVs (>98%) but very low positive predictive values (<13%). Thus, while they are useful for ruling out infection, they should not be used to initiate therapy. In any given ICU, many patients are likely to meet these scores but do not go on to develop invasive candidiasis.

With growing antifungal resistance in *Candida albicans* and *Candida tropicalis*, and the increasing isolation of resistant *Candida* species such as *Candida auris*, antifungal stewardship is crucial. The current study represents a sincere effort in this direction.[4]

A well-conducted, statistically sound study, albeit with a small sample size, demonstrates that withholding antifungal therapy in beta-D-glucan-negative critically ill patients did not impact ICU survival, supporting its role in antifungal stewardship.

This retrospective cohort study analyzed beta-D-glucan-negative ICU patients over an 11-month period. Among 100 patients tested for beta-D-glucan, 53 tested negative. Of these, 22 received antifungal therapy, while 31 did not. While ICU survival was not affected, two patients with *C. auris* in blood cultures had negative beta-D-glucan results. *C. auris* and *Candida parapsilosis* have significantly lower beta-D-glucan levels compared to *C. albicans*. This may lower the sensitivity of the test when these two species are involved.

Bansal et al. demonstrated that stopping empiric antifungals based on a negative beta-D-glucan resulted in savings of 14,000 INR per day per patient.[5] The EMPIRICUS trial, a multicenter, randomized, placebo-controlled trial, investigated whether empirical micafungin therapy increases invasive fungal infection-free survival at day 28 in non-neutropenic critically ill patients with sepsis, multiple *Candida* colonization, and multiple organ failure treated with broad-spectrum antibiotics. It demonstrated that routine empirical treatment with micafungin in critically ill patients with suspected fungal infection did not improve fungal infection-free survival at 28 days.[6]

De Pascale et al. demonstrated that using a beta-D-glucan-guided strategy in septic ICU patients at risk of invasive candidiasis could significantly reduce the use of empirical antifungal therapy without an adverse impact on survival.[7]

Overuse/misuse of antifungals is known to occur in many areas. Asymptomatic candiduria is often treated, even though guidelines

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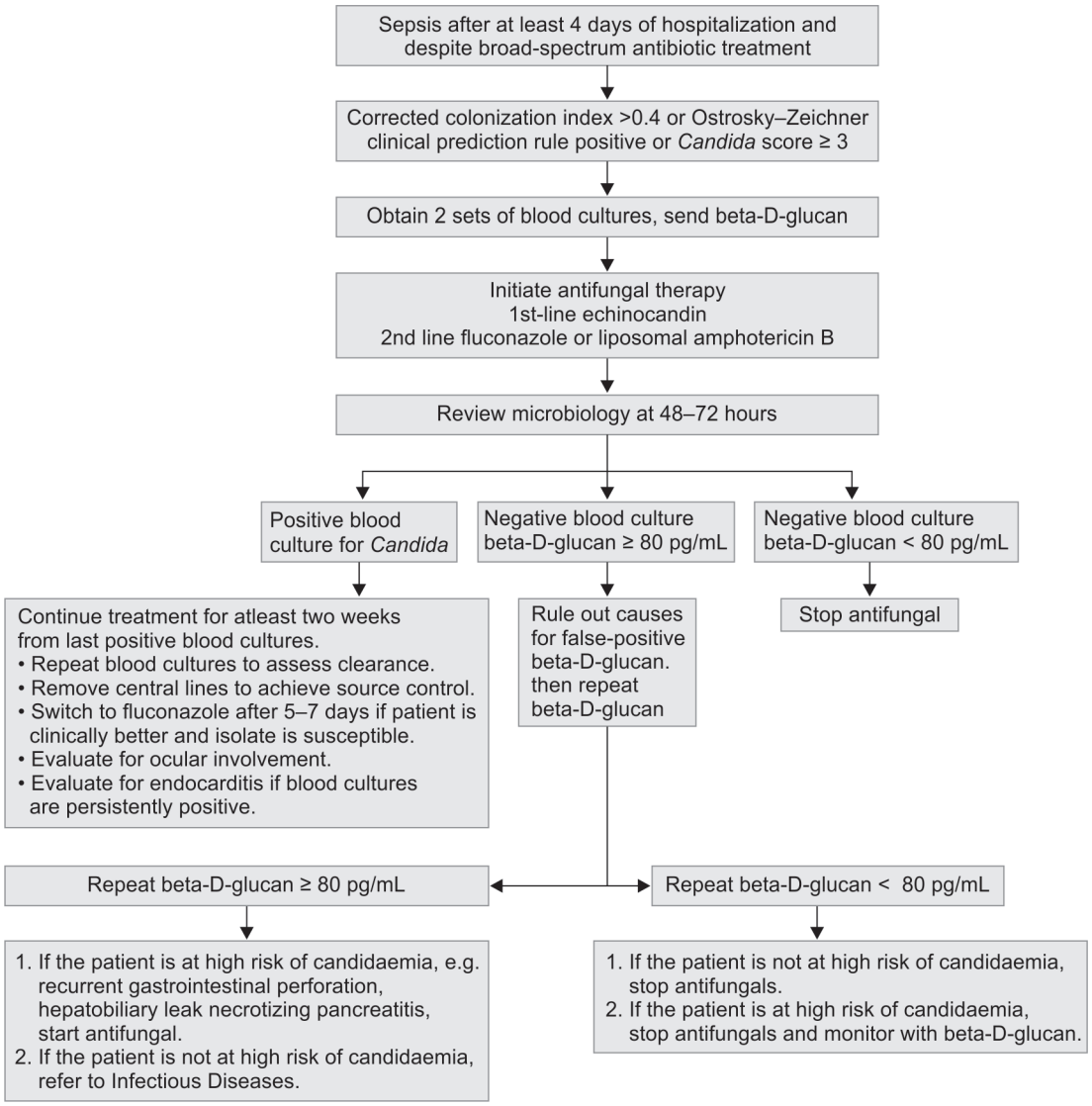

Fig. 1: Algorithm for the optimal management of a septic patient in the ICU at risk of *Candida* infection

clearly state that it should only be treated in neutropenic patients, very low birth weight neonates (weight < 1500 gms), and patients undergoing urologic manipulation.[8] *Candida* in the urine often represents colonization of the perineum and urinary catheter.

Fluconazole is the only triazole that is effective in the urine. Itraconazole, posaconazole, voriconazole, and isavuconazole do not achieve urinary levels. Echinocandins also achieve minimal urinary levels and are not the drugs of choice for urinary tract infections. Amphotericin B deoxycholate and 5-flucytosine are other urinary antifungals that may be used.

In the respiratory tract, *Candida* is almost always a colonizer and should not be treated, despite being isolated from bronchoalveolar lavage samples or tracheal aspirates.[8] This is a strong recommendation with moderate-quality evidence in the IDSA guidelines; however, there is much misuse in this area. We have addressed this problem by not reporting *Candida* spp. in respiratory samples.

Another problem highlighted by studies on antifungal stewardship is the underdosing of fluconazole. In adults, it is important to administer a loading dose of 12 mg/kg on day 1, followed by 6 mg/kg on subsequent days.

It's time we conserve antifungals and utilize them judiciously in our patients if we want to use them successfully in the coming decades. The algorithm below highlights the optimal management of a septic patient in the ICU at risk of *Candida* infection (Fig. 1).

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