MICHIGAN MEDICINE
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RECOMMENDATIONS FOR EMPIRIC TREATMENT OF SUSPECTED INVASIVE CANDIDIASIS IN THE INTESNSIVE CARE UNIT AND FOR THE USE OF THE BETA-D-GLUCAN (FUNGITELL™) ASSAY AS AN ADJUNCT IN THE DIAGNOSIS OF INVASIVE CANDIDIASIS

In patients who have candidemia, delays in the initiation of antifungal therapy have been associated with worse outcomes (Morrell 2005, Garey 2006, Kollef 2012). Blood cultures are not a sensitive diagnostic tool for detecting deep-seated candidiasis not associated with candidemia (Clancy 2013, Tissot 2013). Given these concerns, the early initiation of empirical antifungal therapy is common in ICU patients. This was confirmed by a study that reported that up to 87% of antifungal usage in 4 surgical ICUs was "pre-emptive" or "empiric" (i.e., not for proven infection) (Garey 2006). However, the prevalence of invasive candidiasis in a typical ICU is only ~3%. Thus, thirty-three patients would need to be treated with antifungals to benefit one patient (Clancy 2013). In response, numerous risk factors for invasive candidiasis have been identified and several "*Candida* risk scores" have been proposed (Schuster 2008, Ostosky-Zeichner 2014, Knitsch 2015). The goal of these algorithms is to identify a patient population with a sufficiently high prevalence of invasive candidiasis (≥5%) as to potentially justify empiric/prophylactic use of antifungals (Clancy 2013). Unfortunately, studies evaluating the benefit of early antifungal therapy in high-risk patients (as identified by such "scores") have been hampered by difficulties in enrollment, and thus have been largely underpowered. (Table 1) Because of this, another randomized, controlled trial to definitively prove or disprove the benefit of early antifungal therapy is not likely to be conducted.

Beta-D-glucan (BDG) is a cell wall constituent of many fungi, including *Candida* spp. A commercial assay (Fungitell, Cape Cod Associates, East Falmouth, MA) is FDA approved as an adjunct to the diagnosis of invasive fungal infections, including invasive candidiasis. BDG is not specific for *Candida* spp. and has a sensitivity/specificity of only about 75/80% (Clancy 2014). The BDG assay also reacts with other fungi, including *Fusarium* spp, *Aspergillus* spp and *Pnemocystis jiroveci*. False-positive reactions are common, especially in critically ill patients; causes include IVIG and albumin infusions, Gram positive and Gram negative bacteremias, fungal colonization, use of gauze in wounds, and disruption of the gut mucosa as occurs with abdominal surgery, severe mucositis, and gastrointestinal GVHD, among others (Clancy 2014).

In a recent study of 64 patients admitted to the ICU for ≥ 3 days and expected to require ≥ 2 additional ICU days, 55% of patients developed at least one positive BDG test, but only 1 patient had proven and 5 had probable invasive candidiasis (9% of patients) (Hanson 2012). Thus, the positive predictive value of BDG is poor, even in high-risk patients, but the negative predictive value is quite good (>95%) (Clancy 2013). As described previously, the poor performance of current *Candida* "scores" in identifying patients who would benefit from early therapy has limited their application in clinical practice. BDG has been proposed as a useful adjunct by taking advantage of its excellent negative predictive value. In this way, BDG may be utilized to rule out invasive candidiasis with a high degree of certainty and enable safe discontinuation of unnecessary antifungal therapy. In addition, in combination with an algorithm which adequately identifies high-risk patients, a positive BDG can increase the pretest likelihood of infection to reduce the number needed to treat (Clancy 2013).

Recommendations:

We recommend that BDG be considered in selected ICU patients who have unexplained fever or other signs of infection and who are at high risk for invasive candidiasis. The test should be performed prior to or with the initiation of empiric antifungal therapy and concomitantly with appropriate cultures.

High risk patients are defined as having 2 or more of the following:

- In the ICU ≥3 days, ventilated, receiving broad spectrum antibiotics, have a central line, and have 1 additional risk factor (parenteral nutrition, dialysis, major surgery, pancreatitis, receiving steroids or other immunosuppressive agents)

Discontinuation of empirical antifungal therapy is strongly encouraged in patients with BDG values that are negative (<80 pg/mL). If the baseline BDG value is ≥80 pg/mL, a repeat test is recommended as 2 consecutive serum BDG ≥80 pg/mL are suggestive of invasive candidiasis in high-risk patients. However, positive results should not be utilized as the sole evidence for continuation of antifungal therapy, given the poor positive-predictive value of the test. Infectious Diseases consultation is recommended in such cases.

Rationale for cut-off value:

The manufacturer has assigned the following reference range (http://www.viracoribt.com/Test-Catalog/Detail/Fungitell-1700):

- Negative: Less than 60 pg/mL
- Indeterminate: 60 to 79 pg/mL
- Positive: Greater than or equal to 80 pg/mL

In the Ostrosky study, the mean BDG values were 88.1 (SD, 114.1) pg/mL in patients with no invasive candidiasis, 402.1 (SD, 730.5) pg/mL in patients with probable invasive candidiasis, and 296.6 (SD, 194.3) pg/mL in patients with proven invasive candidiasis. In the Hanson study, median BDG values for patients with proven, probable, or no invasive fungal infection were 103 pg/mL (82–126), 112 pg/mL (84–295), and 28 pg/mL (31–1994), respectively. Thus we recommend that values <80 pg/mL be deemed "negative".
Recent studies of early antifungal use in ICU patients are summarized in Table 1 below.

Table 1: Recent randomized studies of early antifungal use in ICU patients

Inclusion Criteria	Study Groups	Primary Outcome	Secondary Outcomes	Reference
ICU stay ≥4 days, APACHE II score ≥16, 4 days of fever while receiving broad-spectrum antibiotics for at least 4 of the preceding 6 days, and the presence of a central venous catheter	Placebo vs. Fluconazole 800 mg daily x14 days	Resolution of fever, absence of IFI, study drug not stopped due to toxicity, no use of other antifungals. Placebo: 48/127 (38%) FLU: 44/122 (36%) P= 0.78	Documented invasive candidiasis: Placebo: 9% FLU: 5% RR=0.57 [CI= 0.22-1.49] 30-day mortality: Placebo: 17% FLU: 24% (RR= 1.36 [CI= 0.82- 2.24]	Schuster MG et al. Annals Intern Med 2008;149:83-90.
Generalized or localized intra-abdominal infection requiring surgery and an ICU stay	Placebo vs. Micafungin 100 mg daily x6 weeks	Invasive candidiasis: Placebo: 11/124 (8.9%) MICA: 13/117 (11.1%) Difference, 2.24%, 95% confidence interval, −5.52 to 10.20	End of treatment death: Placebo: 1% MICA: 4.3%	Knitsch W et al. Clin Infect Dis 2015;61:1671-8.
In the ICU ≥ 3 days, ventilated, receiving broad spectrum antibiotics, have a central line, and have 1 additional risk factor (parenteral nutrition, dialysis, major surgery, pancreatitis, receiving steroids or other immunosuppressant agent)	Placebo vs. Caspofungin (70 mg-> 50 mg daily) x28 days	Invasive candidiasis: Placebo: 14/84 (16.7%) CASPO: 10/102 (9.8%) P = .14	End of study mortality: Placebo: 15.7% CASPO: 20.5%	Ostrosky-Zeichner L. Clin Infect Dis 2014; 58:1219-26.
In the ICU, mechanically ventilated ≥ 5 days with at least 1 colonization site positive for Candida and at least 1 additional organ dysfunction and > 4 days broad-spectrum antibacterial agents within the last 7 days and 1 arterial or central vein catheter and 1 new finding of ICU-acquired sepsis of unknown origin	Placebo vs. Micafungin (100 mg daily) x14 days	Survival without proven IFI 28 days after randomization: Placebo: 74/123 (60%) MICA: 87/128 (68%) HR= 1.35 (95% CI, 0.87-2.08)	New IFI 28 days after randomization: Placebo: 15/123 (12%) MICA: 4/128 (3%) P= 0.008	Timsit JF, et al. JAMA 2016;316:1555-1564.

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