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Effects of Empiric Antifungal Therapy for Septic Shock on Time to Appropriate Therapy for *Candida* Infection: A Pilot Study

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ABSTRACT

Purpose: Inappropriate initial therapy for *Candida*-related septic shock is common and associated with a high mortality rate. This before-after pilot study was conducted to determine the feasibility of using empiric therapy for reducing the time to appropriate antifungal therapy in patients with *Candida*-related septic shock.

Methods: Patients aged 18–99 years with septic shock presenting to Barnes-Jewish Hospital, St. Louis, Missouri, in 2012–2013 were assigned to 1 of 2 groups. Patients presenting between January 1, 2012, and December 31, 2012, were managed according to local standard of care for patients with septic shock, to include antifungal therapy at the discretion of the treating physician (standard therapy group). Patients presenting between January 1, 2013, and December 31, 2013, received empiric antifungal therapy (primarily micafungin 100 mg/d or fluconazole 800 mg on day 1, followed by 400 mg/d), facilitated by a clinical pharmacist in the medical intensive care unit, until microbiologic cultures were available to determine the cause of septic shock (empiric therapy group). The primary outcome was time to appropriate therapy after shock onset.

Findings: A total of 28 patients were enrolled (mean age, 56.3 [15.1] years [range, 30–92 years]; 16 [57.1%] men). The time to appropriate therapy after shock onset was statistically shorter with empiric therapy (n = 13) compared with standard therapy (n = 15) (10.6 [15.8] vs 40.5 [26.0] hours; $P = 0.001$). Patients receiving empiric therapy were more likely to have received appropriate therapy within 12 hours (69.2% vs 6.7%; $P = 0.001$) and within 24 hours (76.9% vs 40.0%; $P =$ NS) of shock onset. In an analysis to determine the number of septic shock patients needed to be treated with empiric antifungal therapy for 1 patient with *Candida*-related septic shock to receive appropriate treatment, 256 patients without *Candida* infection received a total of 687 doses of empiric antifungal therapy (mean, 2.7 doses per patient) compared with 136 patients who received 382 doses of standard antifungal therapy (mean, 2.8 doses per patient); the number needed to treat was 19.6.

Implications: The present pilot study demonstrated that the use of empiric antifungal therapy for *Candida*-related septic shock was associated with a statistically shorter time to administration of appropriate treatment. ClinicalTrials.gov identifier. (*Clin Ther*. 2014;▮:▮▮▮–▮▮▮) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: antibiotics, *Candida*, outcomes, septic shock.

INTRODUCTION

Inappropriate initial antimicrobial therapy, defined as an antimicrobial regimen that lacks in vitro activity against the isolated organism(s) involved in the infection, can lead to treatment failures and adverse patient outcomes.[1] Several investigations have reported the

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importance of inappropriate therapy as an outcome predictor in patients with sterile-site infections attributed to *Candida* spp, especially when septic shock is present.[2–6] Bassetti et al[7] evaluated data from 216 patients with septic shock attributable to *Candida* bloodstream infection from 5 teaching hospitals in Italy and Spain. Overall, 116 patients (53.7%) died within 30 days from the onset of *Candida* bloodstream infection. On multivariate logistic regression analysis, inadequate source control, inadequate antifungal therapy, and increasing severity of illness, as measured by Acute Physiology and Chronic Health Evaluation (APACHE) II score, were independently associated with a greater risk for 30-day mortality. Initial treatment was considered adequate if the infecting organism was susceptible to the prescribed antimicrobial regimen and if the dosage of the antifungal used was adequate within the first 24 hours after culture positivity.

The study by Bassetti et al[7] supports the findings from the Barnes-Jewish Hospital, where the authors identified 224 consecutive patients with septic shock and a blood culture positive for *Candida*.[6] Overall, in-hospital mortality occurred in 155 patients (63.5%). Similar to the study by Bassetti et al,[7] on multivariate logistic regression analysis, delayed antifungal treatment and failure to achieve timely source control were independently associated with a greater risk for in-hospital mortality. Antimicrobial treatment was classified as adequate if the prescribed antibiotic regimen included an antifungal agent directed against the isolated *Candida* spp and was administered within 24 hours of the onset of septic shock. Despite differences in the definition of *adequate antifungal therapy* between the 2 studies, both studies emphasized the importance of timely treatment with antifungal agents and source control in *Candida*-related septic shock in the optimization of patient outcomes.

The authors performed a pilot study to determine whether the empiric administration of antifungal therapy could reduce the time to appropriate treatment in septic shock attributable to *Candida* infection.

PATIENTS AND METHODS

Study Location and Patient Population

This pilot study was conducted within the medical intensive care units (ICUs; 29 beds) of the Barnes-Jewish Hospital (1250 beds), St. Louis, Missouri. Data were obtained from the electronic medical records of all patients aged 18–99 years with septic shock hospitalized between January 1, 2012, and December 31, 2013, with the exception of patients having a pulmonary source of infection. This ICU averages 1400 admissions per year, with an prevalence of *Candida* as the cause of septic shock being 10%.[8] At Barnes-Jewish Hospital, the rate of resistance to fluconazole in all species of *Candida* combined is ~15%. The resistance rate is greatest (>25%) in *Candida krusei* and *Candida glabrata*, and lowest (<10%) in *Candida albicans*, *Candida tropicalis*, and *Candida parapsilosis*.

Patients receiving comfort care, those with a do-not-resuscitate order, and patients with community-acquired septic shock (eg, from community-acquired pneumonia) were excluded because the occurrence of *Candida* infection in community-acquired septic shock is very low.[9]

The study protocol was approved by the Human Studies Committee at the Washington University School of Medicine in St. Louis.

Study Design and Data Collection

Utilizing a prospective before-after study design, patients with septic shock in the "before" group (those hospitalized between January 1, 2012, and December 31, 2012) were managed according to the standard of care, whereby antibiotic administration, to include antifungal agents, was at the discretion of the treating physician (standard care group). Patients in the "after" group (January 1, 2013, to December 31, 2013) received empiric antifungal therapy (primarily micafungin 100 mg/d or fluconazole 800 mg IV on day 1, followed by 400 mg/d IV), facilitated by a clinical pharmacist (S.T.M., H.A., or P.J.) in the medical ICU, until microbiologic cultures were available to determine the cause of septic shock (empiric therapy group). Clinical pharmacists participated in daily rounds to ensure that the empiric antifungal therapy was administered to all patients with septic shock unless they met the exclusion criteria specified earlier. The choice of antifungal agent was left to the ICU team and the clinical pharmacist but was partly based on whether a patient had any prior exposure to fluconazole, in which case micafungin was prescribed.

The baseline characteristics collected included age, sex, ethnicity, body mass index, comorbidities, and