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Candidemia In the Intensive Care Unit: Does initial antifungal matter? (Editorial)

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One third of all candidemias occur in medical or surgical intensive care units and have all-cause mortality of 50–60% (1–3). It seems intuitively obvious that appropriate treatment is important, so why has it been so difficult to define the best treatment? To answer the question, Garnacho-Montero and colleagues have provided us in this issue with an analysis of a retrospective cohort study from medical and surgical intensive care units in nine Spanish hospitals, data collected from January, 2011 to April, 2016 (4). They found a 30-day mortality of 37.4% if patients with candidemia were treated initially with fluconazole compared to 31.9% if an echinocandin was used initially. However, when they included a propensity score in their multivariate analysis, they found that starting with an echinocandin but not fluconazole was associated with an improved mortality. They also found that patients who were switched from an echinocandin to fluconazole after 3–5 days did better than those who were not, as one would expect if improving patients were switched.

As the authors pointed out, several other retrospective studies of candidemia have not found a difference between initial fluconazole and an echinocandin (5–8), between fluconazole and other therapy (9), or between an echinocandin and either an azole or amphotericin B (10). However, one report found an initial echinocandin superior to fluconazole and another found an initial echinocandin superior to an azole or amphotericin B in patients with an APACHE II score <24 (11, 1). We have only one randomized clinical trial comparing fluconazole with an echinocandin for the treatment of candidemia (12). All-cause mortality within 6 weeks in that study was 31% in the fluconazole-treated group and 23% in the anidulafungin group (difference 8.5%, 95% CI –3.2% to +20.0%, $p=0.13$). With the reasonable expectation that retrospective data is all we have currently, what is the reader to make of the extensive published data? Readers must understand that the overarching problem in discerning an answer for patients in intensive care units is that such patients with candidemia have extensive and variable comorbidities for which it is challenging to control outside of a randomized trial. Presence and management of comorbidities may be a more important

determinate of mortality than drug selection for candidemia. Mortality in comparable patients without candidemia has been only 15% less or, in one study, not different at all (3). If the treatment effect between different drugs is small, it may require a larger study to find it. The Garnacho-Montero study had 234 patients, a substantial number. The advantage of a larger group is in reducing random error, but not necessarily reducing bias. The disadvantage is lack of detail. Case report forms have to use clearly defined baseline factors and endpoints, particularly yes/no answers that are routinely recorded. Facts not routinely recorded in the medical chart cannot be asked, such as factors used in clinical decision making. The reason a physician chose a drug is rarely, if ever, recorded and rarely, if ever, random.

Given the difference between the raw mortality and the propensity-adjusted analysis in the Garnacho-Montero study, how is the reader to interpret the propensity analysis? If two groups are compared who differ only in the choice of drug, as in a randomized trial, a propensity adjustment is unnecessary. The drug choice can be considered an independent variable and tested to determine whether the drug choice was causally associated with a favorable outcome, in unadjusted analysis or by multivariable analysis. However, if drug selection was not independent but dependent on other factors in the individual patient that are independently associated with outcomes, the two groups may not be appropriate to compare. For example, one group might be sicker at baseline and more likely for treatment to fail. To attempt to compensate for these differences in patient selection for each drug, a propensity analysis searches for comparable patients that differ only by treatment, adjusting for baseline factors chosen by the investigators. First, one analyzes differences between the two groups, then one selects several of those baseline factors and calculates a probability, or propensity score, that an individual would have been selected to receive that particular drug. Only factors which were known, observed and recorded in most or all patients can be chosen. Missing data are an ever-present problem. Patients with similar scores can then be compared. This matching requires that the majority of patients receiving one drug can find a match with patients receiving the other drug. Or, as in the case of the Garnacho-Montero analysis, the propensity score can be used as one of the variables (covariates) in a multivariable analysis. The reliability of propensity scores to correct for differences between groups depends critically on how big the differences were between the groups and whether the major factors leading to drug selection were known, recorded reliably and included in the propensity score. Propensity scores, like all adjustments made to observational data, cannot adjust for unknown factors. However, one can test to see how well the chosen factors correlated with drug selection, as was done in the Garnacho-Montero study, but many of the factors leading to the decision to give a drug are interrelated, so that showing the chosen factors correlated with the decision doesn't prove that it was these factors, not interrelated or unknown factors, that influenced the physician's decision. Garnacho -Montero et al. chose the following for the propensity score: age, hematologic malignancy, septic shock, mechanical ventilation and treatment in a hospital where echinocandins were used in more than 50% of patients. Factors not used in the propensity score included SOFA score, APACHE II score, recent surgery and renal replacement therapy (dialysis), though these differed highly between the two treatment groups. Patients given an echinocandin were sicker, had higher SOFA and APACHE II scores, were more often receiving replacement

therapy (dialysis) and more often had recent surgery. In short, propensity scores were a reasonable but imperfect approach for comparing two dissimilar patient groups. The more dissimilar the groups, the less useful is that approach.

The IDSA 2006 guidelines for treatment of candidemia in the nonneutropenic host are of marginal assistance, in that they recommend fluconazole for patients who are not critically ill and who are not likely to have a fluconazole resistant species. In many hospital laboratories, identification of *C. glabrata*, the only common resistant species, occurs no earlier than day 6 or 7, too late to guide initial therapy. The IDSA guidelines also assume that the *in vitro* azole susceptibility predicts patient outcomes of azole therapy and that disease due to *Candida glabrata* responds less well to fluconazole than to an echinocandin. Retrospective studies have not confirmed either assumption. Candidemia due to *C. glabrata* has not responded less to fluconazole when comparable patients were compared (10, 13). Nor has *in vitro* azole susceptibility correlated with patient outcomes of azole treatment in candidemia (14, 2). The existing ambiguity leaves the individual reader to decide whether the existing data on selecting initial treatment of candidemia in intensive care patients are strong enough to influence practice. Although the authors of this editorial do not believe this question settled, our practice based on the available evidence for most critical care patients with candidemia is to begin with an echinocandin and switch improving patients able to take oral medications to fluconazole, dependent on other individual patient factors such as drug-drug interactions, adverse effects, etc. Source control and other key management issues remain more important in improving patient outcomes than which antifungal is chosen.

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