

Management of Invasive Candidal Infections: Results of a Prospective, Randomized, Multicenter Study of Fluconazole Versus Amphotericin B and Review of Literature: A Commentary

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Article: Anaissie EJ, Darouiche RO, Abi-Said D, Uzun O, Mera J, Gentry LO, Williams T, Kontoyiannis DP, Karl CL and Bodey GP. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of literature. *Clin Infect Dis* 1996; 23: 964-972.

Objective: To compare the activities and toxicities of Amphotericin B and Fluconazole in the treatment of presumed or proven invasive candidiasis. *Design:* Prospective randomized multicenter study. *Setting:* Multicenter, involving two private general hospitals, a cancer referral center and a Veterans Affairs Hospital. *Methods:* Patients with documented or presumed invasive candidiasis were included in the study and were randomly assigned by a computer generated sequence of numbers to receive either Amphotericin B or Fluconazole in a stratified manner, according to the peripheral neutrophil count at the time of enrollment of adverse drug-related events. *Results:* One hundred sixty-four patients, sixty of whom were neutropenic were enrolled. Of these, one hundred forty-two (sixty-seven from the Amphotericin B group and seventy-five from the Fluconazole group) were considered evaluable for outcome. These 142 patients were similar with regard to age, sex, underlying disease, presence of central venous catheter, neutropenia, simplified acute physiologic score, use of steroids and broad-spectrum antibiotics, presence of concomitant infections, infecting species, shock, pneumonia, median duration of treatment and type of infection. The overall response rates at 48 hours, after 5 days and at the end of therapy were not significantly different between the Amphotericin B and Fluconazole groups (66% and 64% respectively). There were no differences in response as related to site of infection, pathogen, time to defervescence, relapse or survival rates between the groups. However, adverse events were significantly ($p < .0001$) more frequent with Amphotericin B (42%) than with Fluconazole (5%). *Conclusions:* Fluconazole is effective and better tolerated than Amphotericin B for invasive candidiasis. Its good safety profile, together with the convenience and lower cost of administering oral Fluconazole, perhaps in the outpatient setting suggest that this is the drug of choice for candidal infections caused by fluconazole-susceptible pathogens in hemodynamically stable patients.

COMMENTARY

Invasive candidiasis including hematogenous infection is life-threatening in susceptible patients especially in the hospital setting. It is associated with 38% attributable mortality in the U.S., and is responsible for an important reason for prolonged hospital stay. In the Philippines, invasive candidiasis is also fast becoming one major nosocomial infection.

A number of factors hinder successful management of this infection. Foremost among these problems: the limited ability to isolate candida organisms in the blood, so that in most instances, empiric antifungal treatment is resorted to.

Amphotericin B, the accepted standard anti-fungal for invasive infections is known for its high incidence of drug-related toxicity and its high cost. A relatively new but well-tolerated drug, fluconazole raises concerns about its role in serious candidal infections since it only possesses fungistatic activity and has limited activity against certain *Candida species*. Some clinicians have thus questioned whether it can safely substitute for Amphotericin B.

This study was conducted with the aforementioned important concerns in mind. The patient assignment was randomized in a stratified fashion in all the centers, which participated in the study. The investigators first classified patients to subgroups they deemed would likely influence the outcome measures of interest. They were first stratified according to peripheral neutrophil counts thus, $<1,000$ in one group and $>1,000$ neutrophils/mm³ in the other. After which, these two groups were further stratified into type of invasive candidal infection namely: blood/disseminated, organ candidiasis and presumed candidiasis. In each of these types, patients

were then randomized to receive either Amphotericin B or Fluconazole. Such a process helped ensure that there were a comparable number of patients who received the drugs under trial as stratified to subgroups.

Of the original 160 enrollees, only 142 were evaluable. An equal number (seven each) randomized to the two drugs of interest were non-evaluable. The treatment groups had similar baseline data except for the drug to which they were assigned to receive. Follow-up and analysis were noted to be complete for the 142 patients. If we go by the principle of "once randomized, analyze," this study did not present real intent-to-treat data although the investigators have mentioned reasons to justify why only 142 patients were included in their intent-to-treat analysis.

The best way to avoid biases is double-blinding. Blinding is important for the assessment of outcome and to avoid possible co-intervention. Although the investigators mentioned that randomization was done in a blinded fashion, blinding was not maintained in this study because of the inherent differences between the physical characteristic of the two drugs. However, the results of this study are still valid even if blinding was not maintained, because the assessment of outcomes utilized objective parameters. For instance, a patient was labeled to have responded only when there was disappearance of all clinical (i.e. fever, hypotension, tachycardia etc) and laboratory (i.e. hematologic evaluation, cultures etc) indicators of infection. To assure the reader however that the patients in each treatment group were treated equally, the study should have mentioned whether or not certain maneuvers (example, how many percent had their catheters removed?) or adjunctive therapy (example, how many received GCSF?) other than the study drugs, which could be considered co-interventions, were given.

The primary outcome analysis was a comparison of response rates between the Amphotericin B and Fluconazole groups. In our preoccupation with death, considerable emphasis is given to survival and mortality but very little attention to response to treatment and morbidity/adverse reactions.

Sample size calculations were based on a power of 80% and an alpha level of 0.05 was used. Response rates were comparable at 66% and 64% respectively and a p value of 0.84. With the limitation of sample size recognized by the investigators, they have acknowledged and thoughtfully cautioned the reader regarding the possibility of a type II error. Given this information, power calculations were done. True enough, this study gives only 14% probability that if there was really difference, it would be detected, estimate was correct, thus a low power.

What if this study enrolled 1,000 patients in each treatment arm? Further calculations were done for purposes of comparison. This is the only time that the power improved to 80%. In such instances when a valid study lacks power, all is not lost. A meta-analysis could be done. The investigators, combining results of this trial and results of another matched cohort study, attempted this. However, the results could not be relied on as valid since this meta-analysis involved two studies with different study designs.

With the said limitation in mind, I agree with the investigators that even if the conclusions held true for all patients in this study, they may not necessarily apply to certain patient subgroups like those who are infected with different Candida species and those with very poor prognosis factors.

Finally, taking this study in its totality - with its concerns addressed as well as its limitations, and unresolved issues, this is a good valid study. It has taken into consideration important issues of response/morbidity and adverse reactions as well as survival and mortality. The results are applicable to patients we see in the Philippines. The study has shown that Fluconazole is comparable to Amphotericin B in terms of efficacy in non-neutropenic patients with serious candidal infections due to susceptible organisms. To these patients, Fluconazole can be recommended as a safer, less toxic alternative to Amphotericin B. In addition, local queries comparing cost indicate lesser treatment expense with Fluconazole. This is an important added advantage especially for Filipino patients and those in other developing countries.

RECOMMENDATIONS

- A) Future randomized controlled trials involving Amphotericin B and Fluconazole preferably with a larger sample size to resolve the following issues: 1. Comparison of efficacy in certain patient subgroups such as other immunocompromised patients, and those with Candidiasis caused by non-albicans; 2. dosage and duration of therapy for Fluconazole for the different risk group categories.
- B) A metaanalysis should be done on existing randomized controlled trials to address some of the aforementioned concerns for the different subgroups of patients.