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Reply to "Risk for Invasive Fungal Infections during Acute Myeloid Leukemia Induction Therapy: a True Association with Echinocandins?"

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We acknowledge the letter of Marini and colleagues (1), in which the authors raise several issues with regard to our epidemiological analysis of invasive fungal infections (IFIs) among patients receiving antifungal prophylaxis during initial remission induction chemotherapy (RIC) for acute myeloid leukemia (AML) (2). Specifically, they suggest that our findings are inconsistent with those of randomized control trials (3) because we did not observe a difference in the incidences of IFI among patients receiving mold-active triazoles versus those receiving fluconazole in the first 42 days after RIC. Second, they hypothesize that the higher rates of IFI observed with echinocandin prophylaxis may be explained by the timing and characteristics of patients selected to receive these agents, which were not given due attention in our analysis. They correctly note that echinocandins were used for prophylaxis in our study group predominantly during the first 20 to 30 days of RIC, possibly to avoid drug interactions and increased toxic interactions with chemotherapy. In contrast, mold-active triazoles, which are available in both intravenous and oral formulations, were more likely prescribed after the first 10 to 20 days of induction chemotherapy, when the risk of breakthrough IFI may be lower.

We believe that the authors' first point regarding a lack of difference in the rates of IFI between patients receiving mold-active agents and fluconazole during the first 42 days misrepresents the data presented in the paper. We did not specifically compare breakthrough IFI rates between patients given fluconazole and mold-active azoles during the first 42 days of RIC because fluconazole was infrequently administered during this initial high-risk period. The data presented in Table 2 of our paper are for all IFIs (yeasts and molds) at 120 days of RIC and cannot be used to infer a lack of difference in IFIs, particularly mold infections, during the first 42 days.

With regard to the authors' second point, we refer them to our subsequent paper also published in this journal (4), where we examined disease, toxicity, and chemotherapy-related confounding variables that may contribute to higher rates of IFI in echinocandin prophylaxis patients. In this study, we analyzed hospitalization, neutropenia, underlying malignancy remission rate, and antifungal prophylaxis as time-dependent variables using multivariate Cox regression models for IFI development and survival. These models included other potential disease and chemotherapy-related confounders identified in the univariate analysis. We found that receipt of a clofarabine-based remission induction regimen (frequently used for older patients and those with poor-prognosis AML) and echinocandin prophylaxis were the only two independent risk factors for breakthrough IFI risk during the first 120 days of RIC. Percentages of patients on clofarabine-based RIC were similar between patients receiving echinocandin and those receiving voriconazole-posaconazole prophylaxis (26% versus 24%, $P = 0.8$). No other malignancy or chemotherapy-related covariates that accounted for the higher IFI breakthrough rates in the echinocandin prophylaxis population could be identified.

In a larger context, our tandem papers (2, 4) exemplify the problems of applying data from prospective clinical trials to the clinical setting. In daily practice, clinicians must treat older patients with more advanced hematological malignancies and organ dysfunction, who would be excluded from clinical trials. Indeed, Herbrecht and colleagues (5) estimated that approximately one-quarter of patients treated for invasive aspergillosis in daily clinical practice would not be considered for inclusion in therapeutic clinical trials because of organ dysfunction or their malignancy status. Similarly, only a small portion of cancer patients with candidemia are eligible to be enrolled in clinical trials (6). Therefore, we think that large single-center epidemiological studies that include sicker patients and "real life" antifungal usage patterns can provide useful data and may identify important clinical patterns, such as higher IFI breakthrough rates associated with echinocandin prophylaxis, which should be verified in multicenter, prospective epidemiologic or therapeutic studies.

REFERENCES

1. **Marini BL, Perissinotti AJ, Huang AM, Frame DG, Kaul DR.** 2014. Risk for invasive fungal infections during acute myeloid leukemia induction therapy: a true association with echinocandins? Antimicrob. Agents Chemother. **58:**4988–4989. http://dx.doi.org/10.1128/AAC.03044-14.
2. **Gomes MZR, Mulanovich VE, Jiang Y, Lewis RE, Kontoyiannis DP.** 2014. Incidence density of invasive fungal infections during primary antifungal prophylaxis in newly diagnosed acute myeloid leukemia patients in a tertiary cancer center, 2009 to 2011. Antimicrob. Agents Chemother. **58:** 865–873. http://dx.doi.org/10.1128/AAC.01525-13.
3. **Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh Y-T, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D.** 2007. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N. Engl. J. Med. **356:**348–359. http://dx.doi.org/10.1056/NEJMoa061094.
4. **Gomes MZR, Jiang Y, Mulanovich VE, Lewis RE, Kontoyiannis DP.**

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2014. Effectiveness of primary anti-aspergillus prophylaxis during remission induction chemotherapy of acute myeloid leukemia. Antimicrob. Agents Chemother. **58:**2775–2780. http://dx.doi.org/10.1128/AAC.01527-13.

5. **Herbrecht R, Bories P, Moulin J-C, Ledoux M-P, Letscher-Bru V.** 2012. Risk stratification for invasive aspergillosis in immunocompromised patients. Ann. N. Y. Acad. Sci. **1272:**23–30. http://dx.doi.org/10.1111/j.1749-6632.2012.06829.x.
6. **Kontoyiannis DP.** 2009. Echinocandin-based initial therapy in fungemic patients with cancer: a focus on recent guidelines of the Infectious Diseases Society of America. Clin. Infect. Dis. **49:**638–639. http://dx.doi.org/10.1086/603585.