Open Forum Infectious Diseases
RESPONSE TO LETTER TO THE EDITOR

Reply to Collis et al.

Keywords. antifungal resistance; candidemia; clinical predictive model; fluconazole.

To the Editor—We thank Collis et al [1] for their considerate letter to the editor presenting an external validation of our clinical predictive model (CPM) for fluconazole resistance in patients with *Candida* bloodstream infections [2]. Despite the increasing importance of *Candida* antifungal resistance, the only method approved to evaluate resistance is antifungal susceptibility testing. The lack of accessible methods to assist clinicians in community hospitals where susceptibility testing is not routinely performed results in extended use of echinocandins and prolonged hospitalizations. Our model estimates the risk of fluconazole resistance to identify patients who would be appropriate to receive fluconazole as initial or step-down oral therapy, using 5 readily available clinical parameters: older age, history of bone marrow transplant/stem cell transplant, myelodysplastic syndrome, prior bacterial bloodstream infection, and exposure to azoles.

Collis et al [1] conducted a validation of our model using a cohort from an academic center in Australia. When our model was applied to this cohort, the C statistic was 0.727, compared with the original value of 0.788. Variability is expected in external validation owing to heterogeneity in predictor effects, but both results indicate good discrimination. The smaller sample size (of the validation cohort 111 patients) may have influenced the performance of the model. In general, >200 events are preferred in validation studies [3, 4]. Furthermore, the prevalence of fluconazole-resistant isolates was higher in the validation cohort (22.5% vs 13.4%). As mentioned by the authors, local epidemiology can be crucial, as the geographic distribution of fluconazole resistance can alter generalizability of our study.

Collis et al [1] also created an alternative model including additional variables using backward stepwise logistic regression in 1000 bootstrapped samples. Internal validation of this model was conducted appropriately using the preferred method of bootstrap resampling [5, 6]. However, there are a few concerns regarding the selected variables. First, we emphasize in our model the inclusion of readily available risk factors at time of treatment initiation. CPMs that use variables uncommonly available may achieve better fit and higher C statistics but are impractical for everyday use and can affect its accuracy [7, 8]. Certain variables in the alternative model may pose challenges in obtaining them. For instance, *Candida* species is insufficient to predict susceptibility patterns, and initial therapy is often started based on the presence of yeast in cultures, with the species remaining unknown at that time [9, 10].

In addition, we prioritized clinical plausibility over *P* values of individual variables, and the same criteria were used to select variables when assessing multicollinearity. Selection of predictors by statistical significance alone is known to produce selection bias and optimism [7]. Some of the selected variables in the alternative model may not be clinically relevant or have high collinearity. For example, *Pneumocystis jirovecii* pneumonia prophylaxis was included, which when used in our data set is highly collinear with hematologic cancers such that the 2 variables "knock each other out," leaving both insignificant and the model poorer for it. In development of CPMs, clinical plausibility and the overall performance are more important than significance of individual variables. This is doubly true in smaller data sets, because the *P* value is highly dependent on sample size; with only 25 patients with fluconazole resistance, the data set has severe limitations in its ability to discriminate >2–3 variables at a time. Thus, our model likely would perform just as well in a future cohort of patients from Melbourne or another locality.

Collis et al [1] demonstrated that our model had a similar discrimination (C statistic = 0.727) as the alternative model (C statistic = 0.747), especially when considering the instability of small sample sizes and the inherent optimism that exists when the same data set is used to train and validate the model. Bootstrapping improves optimism, but it is still more optimistic than external validation. After all, the C statistic of our model decreased from 0.788 to 0.727 on external validation after similar bootstrapping.

In conclusion, CPMs are becoming an integral part of medical practice but before implementation external validation is imperative, and we strongly welcome the work done by Collis et al and thank them for the great work done. The selection of potential predictors that are universally and uniformly defined, measured, and available across sites is an important aspect of building a CPM, ultimately affecting its generalizability and usefulness. We agree with the authors that local epidemiology, antifungal use, and host factors can cause variability and that there will always be a component of confounding and collinearity. We encourage further external validation and iterative development of our model to assess its generalizability with the goal of future implementation to use fluconazole as an early and optimal alternative for treatment of candidemia.

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