Candida glabrata and *FKS* Mutations: Witnessing the Emergence of the True Multidrug-Resistant *Candida*

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(See the Major Article by Alexander et al on pages 1724–32.)

Keywords. *Candida glabrata*; multidrug-resistant *Candida*; echinocandins; *FKS* mutation.

The term "multidrug-resistant *Candida*" has been used loosely in the mycology literature since the early 2000s [1–4]. In 2009, the Clinical and Laboratory Standards Institute subcommittee on antifungal susceptibility testing formally adopted the term, defining multidrug resistance in *Candida* as resistance or lack of susceptibility to at least 1 drug in 2 or more antifungal classes (unpublished data). Up until recently, this was little more than an academic exercise, as these isolates were usually found buried within very large epidemiologic surveys or in case reports [1, 5, 6]. Case in point: In a recent population-based study of candidemia in the United States, Cleveland et al [7] reported a 7% incidence of fluconazole resistance, 1% incidence of echinocandin resistance, and 0.4% incidence of both echinocandin and fluconazole resistance (8 of 9 isolates were *Candida glabrata*).

The molecular mechanisms of echinocandin resistance were described in parallel to the development of the first echinocandins [8]. Early descriptions were focused on the *FKS1/ETG1* mutations [9, 10] and over the years clinicians were reassured because these mutations were, for the most part, created in the laboratory to study resistance and mechanisms of action and because when sporadically found in clinical isolates, correlation with both minimum inhibitory concentrations (MICs) and clinical outcomes was poor [11].

In this issue of *Clinical Infectious Diseases*, Alexander et al [12]. present a very elegant retrospective study studying 293 episodes of candidemia caused by 313 strains of *C. glabrata* over a 10-year period at a large tertiary care center. They describe fluconazole resistance increasing by 50% and echinocandin resistance nearly tripling over the study period. Most important, they describe 11 isolates (3.5%) that were resistant to both fluconazole and echinocandins. They also describe 25 isolates (7.9%) that harbored an *FKS* mutation, and among those, 64%–68% were found to have MICs against echinocandins that would qualify them as nonsusceptible. In the final analysis, the authors found that among patients treated with echinocandins, microbiological cures were very good (>89%) irrespective of the echinocandin susceptibility results. However, when assessing only the episodes of patients with MICs showing resistance and harboring the *FKS* mutations, the authors found universal lack of response. Independent predictors of mortality at 30 days were prior azole therapy, treatment with polyenes, end-stage liver disease, malignancy, and intensive care unit status. Not surprisingly, the predictors of fluconazole and/or echinocandin resistance were previous exposure to the agents.

The results of Alexander et al [12] should be approached carefully because they are limited by the number of observations and the actual frequency of *FKS* mutations, as well as the fact that they may strongly reflect local epidemiology and the outcomes of local practice patterns. It is important to also consider that neither susceptibility patterns alone nor the presence of *FKS* mutations alone correlated strongly with outcome and that in their cohort, previous treatment with azoles or polyenes was significantly associated with failure, highlighting the role of echinocandins in these infections.

However, Alexander et al [12] highlight the emergence of these types of strains and showcase the need for systematic susceptibility testing and further phenotypic and genetic surveillance tied to patient outcomes. They also help solidify

Received 20 February 2013; accepted 25 February 2013; electronically published 13 March 2013.

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Clinical Infectious Diseases 2013;56(12):1733–4

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DOI: 10.1093/cid/cit140

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what the literature has been hinting at for a few years now: that *C. glabrata* continues to be the "problem child" and that it will most likely represent the bulk of multidrug-resistant isolates (with documented resistance against not only azoles and echinocandins, but polyenes as well [13–18]), challenging clinicians with the most significant therapeutic dilemmas.

Note

Potential conflicts of interest. The author is a consultant/advisor/speaker for and receives research funding from Merck, Astellas, and Pfizer.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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