Fluconazole Prophylaxis in HIV Disease, Revisited

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(See the article by Goldman et al. on pages 1473–80)

Goldman et al. [1] approach the question of emerging drug resistance associated with ongoing fluconazole prophylaxis for mucosal candidal infection in HIV disease. After a median of ~2 years of follow-up, the proportion of oropharyngeal and/or esophageal infections that were clinically refractory or resistant to fluconazole was higher among patients receiving continuous fluconazole therapy (9%) than among those receiving episodic fluconazole therapy (2%), but the risk of any infection was 4 times greater in the latter group. As a result, the risk of a clinically refractory or resistant oropharyngeal and/or esophageal candidal infection was essentially the same in both groups, at slightly more than 4%. The median MICs of fluconazole increased 2-fold in the episodic fluconazole arm and 3-fold in the episodic fluconazole arm, but many of these patients were receiving treatment for several years. These results, coupled with the fact that there is no general risk to microbial ecology from the use of fluconazole, indicate that concern about resistance should not be a factor in the decision to provide prophylaxis.

With this new information, and because generic fluconazole is available at ~10% of the price of the branded drug, reassessment of the use of prophylaxis against mucosal *Candida* infection in HIV-infected persons is timely. Because these infections are so common, the number needed to treat with continuous therapy to prevent 1 infection per year is only 1.5 patients. On the other hand, what this policy would really mean is the addition of another drug to every such patient’s regimen and to the system’s burden, to reduce the typical number of infections per patient by one-half of an episode each year. Given this small absolute effect, adoption of continuous prophylaxis for mucosal disease as an indiscriminate policy would seem to be imprudent, even with the newly lowered acquisition costs. However, few patients are typical: the number of infections per patient will vary from 0 to many. The authors do not provide analyses stratified by prior frequency or esophageal candidal infection was essentially the same in both groups, at slightly more than 4%. The median MICs of fluconazole increased 2-fold in the episodic fluconazole arm and 3-fold in the episodic fluconazole arm, but many of these patients were receiving treatment for several years. These results, coupled with the fact that there is no general risk to microbial ecology from the use of fluconazole, indicate that concern about resistance should not be a factor in the decision to provide prophylaxis.

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Also of importance is the fact that this study confirms the potency of fluconazole prophylaxis in cutting the risk of invasive fungal infection by one-half and the risk of deep fungal infection by two-thirds. As the authors point out, the effect size is similar to that found in prior studies, even though Goldman et al. [1] used thrice-weekly rather than the daily dosing used by Powderly et al. [2]. As noted by the previous investigators, this effect is not a sufficient reason to administer fluconazole prophylaxis in Western countries because of the low underlying risk of disease. The number needed to treat with continuous therapy to prevent 1 invasive or deep infection per year would be >60 and >100, respectively.

This could be quite different in a non-Western setting. For example, in the Ugandan cohort study cited by the authors, cryptococcal disease occurred at a rate of 40 cases per 1000 patient-years [3]. It was also highly lethal: one-third of the cohort died, and one-fifth of these persons died of cryptococcosis. If the effect size for continuous fluconazole treatment were the same in the Ugandan cohort as it was in Goldman et al. [1], the numbers needed to treat to prevent 1 invasive or deep infection per year would be a much more reasonable 18 and 12 patients, respectively. Adequate clinical trials are needed to determine the effect size in less developed African and Asian settings. If these trials show fluconazole to be effective, donated or generic fluconazole might well join interventions such as trimethoprim-sulfamethoxazole therapy and mosquito nets as important adjuncts or temporizing measures in less developed countries. Absent reasons to believe that fluconazole will be ineffective in these settings, use of prophylaxis in high-incidence areas is not unreasonable at this time.
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References

