



Antifungal Resistance : How Big is the Problem?

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Microbiological resistance to antifungals, particularly azoles, has been increasingly reported. Despite the increase in frequency of resistance, reports of clinical antifungal failures or single stains becoming resistant to antifungal therapies remain distinctly uncommon. Recently NCCLS guidelines for susceptibility testing of yeasts and moulds have been approved. In addition, other methods, such as agar based screening techniques, colorimetric assays and the E-test have also been used for assessing susceptibility. With the increased availability of antifungal susceptibility testing it is important to assess the clinical significance of antifungal resistance and to develop strategies for optimizing use of these procedures. The presence of less susceptible yeasts in oropharyngeal candidiasis, particularly with species other than *Candida albicans*, is common but clinical responses to azoles remain excellent. Prior to the advent of highly active antiretroviral therapy, antifungal resistant oropharyngeal yeasts were common. We assessed the frequency and significance of fluconazole resistance in recurrent oropharyngeal candidiasis in a longitudinal study in patients with advanced HIV-infection. Chromogenic agar with fluconazole was used to increase detection of fluconazole resistant and non-albicans yeasts. In this study of 59 patients, resistant yeasts (defined as an MIC > 16) were detected in 50/155 (32%) symptomatic episodes of thrush. Clinical responses to fluconazole occurred in 151/155 (97%) episodes, although fluconazole doses >100 mg/d were used in 33/50 (66%) of episodes with yeasts having MICs \geq 16 as compared to 24/120 (20%) episodes with MICs < 16. In other clinical settings of patients at high risk for serious fungal infection, including patients undergoing bone marrow and organ transplantation, azole resistance remains uncommon, particularly in *Candida albicans*. Azole prophylaxis in those patients has significantly reduced serious *Candida* although species with decreased susceptibility or resistance have been reported. In highly immunosuppressed patients and in patients with fungemia and other deep sites of infection, antifungal resistance has important clinical consequences. The empiric use of azoles for the treatment of serious *Candida* infections has been used in the management of patients at high risk for infection because the diagnosis of invasive candidiasis is difficult and is associated with high mortality. In such patients the dose of azole therapy should be chosen to adequately treat serious infection but may need to be changed or increased in patients with less susceptible yeasts such as *Candida glabrata*.

Recently the fungal armamentarium has expanded to include the echinocandins as well as newer triazoles, such as voriconazole, ravuconazole and posaconazole, which possess an expanded spectrum of activity that includes resistant yeasts such as *Candida krusei* and *Candida glabrata*. While the newer azoles have only limited clinical studies supporting their use in serious *Candida* infections due to these organisms, they possess excellent activity in vitro and in animal models of *Candida* infection. Notably, while the in vitro activity of these drugs is significantly better than fluconazole against many of these strains, there is a linear relationship between the MICs of voriconazole and those of fluconazole so that organisms highly resistant to fluconazole will have an increased MIC to voriconazole as well, although the breakpoints for susceptibility have not been established.

The echinocandins offer potential fungicidal activity against *Candida* species, including fluconazole-resistant and -susceptible strains, as well as yeasts other than *Candida albicans*. Only a few species have increased MICs, such as *Candida parapsilosis*, although the clinical significance of those findings are not clear. While resistance through mutation in the target enzyme has been reported, the development of resistance on therapy thus far has been limited and the role of testing yeasts for susceptibility to this class of compound has not yet been established.

For most yeasts, it is more important to devote resources to the species level identification than it is to perform actual susceptibility testing. For example, the isolation of *Candida krusei* will be inherently resistant to fluconazole yet susceptible to amphotericin, the echinocandins and newer azoles, such as voriconazole. For some isolates, particularly *Candida glabrata* or for persistent infection or breakthroughs with azole prophylaxis, susceptibility testing may be of clinical value.

The importance of antifungal resistance in moulds to date has been a limited clinical problem. While resistant *Aspergillus* species have been reported, only a limited number of strains have been tested in this setting and it is not clear how widespread this issue is clinically. Notably, cross-resistance between itraconazole and posaconazole has been reported which could be of clinical importance, as voriconazole susceptibility was maintained. Some *Aspergillus* species, especially *Aspergillus terreus* are frequently resistant to amphotericin B so that the newer azoles may be the drug of choice against that organism. More frequent has been the isolation of less susceptible or resistant fungi, such as the Zygomycetes, which are resistant to most azoles, and *Scedosporium apiospermum* or *Fusarium*, which are both frequently resistant to amphotericin B and susceptible to the newer azoles. In those settings as in the case of *non-albicans* yeasts, identification to the species level is more important than the actual performance of susceptibility testing.

The number of serious invasive fungal infections has continued to increase due to the fact that more immunosuppressed patients are at risk for these infections. Fortunately, the antifungal agents against these organisms have also increased with more effective and less toxic alternatives. Clearly the importance of clinical resistance continues to increase so that the injudicious use of antifungals should be avoided. Adequate dosing and targeted use of azole therapy will optimize the utility of these agents in the therapy of invasive fungal infection and will keep antifungal resistance a manageable clinical problem.

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