Azole drug resistance in *Candida* species

*Candida albicans* is found in the mouth and gastrointestinal tract of a significant proportion of the normal human population. This opportunistic pathogen can cause deep-seated infection, which may be localised or disseminated, but is more often seen causing mucosal or cutaneous infection. Although *C. albicans* remains the predominant cause of all forms of human candidosis, *C. tropicalis* has emerged as an important pathogen in neutropenic patients and *C. parapsilosis* infection is common in individuals receiving parenteral nutrition. Other *Candida* species have also been recognised as significant pathogens.

Imidazole and triazole compounds are amongst the most useful drugs for the treatment of human candidosis. They inhibit the C-14 a-sterol demethylation step in the formation of ergosterol, leading to accumulation of methylated sterols which disrupt fungal membrane structure. The earliest members of this large group of drugs, clotrimazole and miconazole, are useful for topical treatment of superficial candidosis and this has remained the case for most of the similar imidazole compounds that have appeared since. However, some more recent compounds, such as ketoconazole and the triazoles fluconazole and itraconazole, are effective after oral administration and can be used to treat both superficial and deep-seated infection.

Although azole antifungal agents have long been in widespread use, there have been few verified reports of resistant strains of *C. albicans* emerging during treatment. The low incidence of clinical resistance has been attributed to the fact that *C. albicans* is a diploid fungus with no haploid sexual stage. Thus, unless resistance is a dominant character, resistant strains will seldom appear. Until 1986, the few resistant strains of *C. albicans* that had been isolated had all been from patients who had received long-term oral treatment with ketoconazole for the uncommon condition, chronic mucocutaneous candidosis, which had relapsed in each case despite adequate blood concentrations of the drug. It is not surprising that these initial reports were disputed, given the extent to which the results of MIC determinations with ketoconazole depend on the conditions under which the tests are done. However, extensive testing of these strains of *C. albicans* has confirmed that they are much less susceptible to a range of azole drugs than other strains of this species. At least two mechanisms of resistance are evident. In one, the azole drug fails to cross the cell envelope. In the other, azole-induced blockade of the C-14 sterol demethylation step in the formation of ergosterol is circumvented.

Mucosal forms of candidosis are some of the most common and persistent infections in individuals with HIV infection. Many AIDS patients require long-term treatment for suppression of oral or oesophageal candidosis. Oral ketoconazole has been used widely, but treatment failure and relapse have been common. Although this has usually been associated with malabsorption of the drug in AIDS patients, MIC data have sometimes suggested drug resistance as the cause. The triazole drug fluconazole is less toxic and better tolerated than ketoconazole, and is absorbed more reliably. It has been shown to be more effective than ketoconazole in controlling oropharyngeal candidosis in AIDS patients. However, one consequence of the long-term use of fluconazole has been a marked increase in the number of reports of AIDS patients with persistent oral or oesophageal candidosis, apparently because of drug resistance.

As with ketoconazole, the results of MIC determinations with fluconazole must be interpreted with caution because the conditions under which the tests are performed have a marked effect on the results. For this reason, a high MIC on its own is not proof that treatment failure or relapse is due to drug resistance. More convincing evidence is the demonstration that the MIC for the most recent candida isolate is higher than that for isolates obtained earlier during treatment. If the latter have not been retained, it is important to test clinical isolates in parallel with sensitive and resistant reference strains of the same *Candida* sp. Most of the recent reports of apparent resistance to fluconazole of *Candida* spp. from AIDS patients have been based on isolated MIC determinations on strains obtained after treatment had failed; few have included comparisons with either earlier isolates from the same patient or with control strains.

In the case of *C. albicans* isolates from AIDS patients who failed to respond to treatment with increasing doses of fluconazole, MICs of ketoconazole and itraconazole have sometimes been found to be much lower than those of fluconazole. Less than ideal test conditions could account for these findings. Another explanation is selective resistance to fluconazole, but this seems less plausible because all azole antifungals have a similar mechanism of action.

In contrast to the long periods of treatment needed to induce azole resistance in *C. albicans*, short courses of fluconazole treatment have proved sufficient to induce resistance in *C. glabrata* (*Torulopsis glabrata*). Unlike *C. albicans*, this organism is haploid and this could explain the rapid development of clinical resistance noted in several recent reports. In one reported case, a *C. glabrata* isolate showed a 30-fold rise in...
fluconazole MIC after 9 days of oral treatment; further investigation indicated that this isolate was cross-resistant to itraconazole and ketoconazole. It is unclear whether resistance emerged as a result of the selection of a pre-existing sub-population of resistant organisms, or whether it was due to the development of drug-resistant mutants during treatment. The mechanism of resistance in C. glabrata appears to involve failure of the drug to penetrate the cell envelope (unpublished observations).

Another source of concern arising from the widespread use of fluconazole has been an apparent increase in the prevalence of colonisation and infection with intrinsically less sensitive yeasts, such as C. krusei. Fluconazole MICs for this species are, unlike C. albicans, often high before treatment. Recent case reports have described the failure of the drug to suppress C. krusei infection. Other reports have suggested a higher incidence of both colonisation and infection with C. krusei among neutropenic patients who had received fluconazole than among similar patients who had not. Increased colonisation with C. glabrata was also noted in those receiving fluconazole, but there was no increase in the number of infections caused by this organism. In contrast, the number of serious infections caused by C. albicans and C. tropicalis was significantly lower in patients receiving prophylactic fluconazole. Treatment failure, attributable to the development of azole-resistant C. albicans strains, appears to be becoming more common, but still seems to be confined to patients receiving long-term treatment. In view of the increasing number of individuals requiring this form of management and the apparent potential of such treatment to select for resistance, it is becoming more important to document the magnitude of the problem and investigate the effects of changing prescribing practices. In the meantime, it must not be assumed that the development of fluconazole resistance among C. albicans strains during treatment is a characteristic of this particular drug not shared with other azole compounds. Until it is proved otherwise, it must be regarded as an inevitable consequence of prolonged drug use. The rapid development of drug resistance in patients with C. glabrata infection and the persistence of C. krusei infection observed in patients treated with fluconazole is also of concern and highlights the need for accurate identification of organisms before commencing treatment.

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References