Candida krusei infections and fluconazole therapy

LP Samaranayake

Candida species are by far the most common agents of mucosal fungal infection in man. While Candida albicans is the most notorious pathogen in this group, non-albicans species such as Candida krusei are gradually emerging as pathogens of concern, especially in compromised hosts. It is thought that the wide use of the newer triazole drug, fluconazole, in HIV-infected individuals is contributing to this phenomenon. Studies in both humans and animals have now demonstrated prophylactic and therapeutic failure of fluconazole against C. krusei due to increasing resistance of the organism to thisazole. Thus, the indiscriminate use of fluconazole, a drug with relatively minimal toxicity and excellent pharmacokinetics, may lead to the development of widespread resistance to thisazole among Candida species.

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Early reports of C. krusei in humans describe the organism as a transient, infrequent isolate of minor clinical significance inhabiting the mucosal surfaces.1 More recently, it has emerged as a pathogen with biological properties that differ from C. albicans2 and has a spectrum of clinical manifestations such as fungaemia, endophthalmitis, arthritis, and endocarditis, most of which usually occur in compromised patient groups in a nosocomial setting.3 The widespread use of the newer triazole, fluconazole, to suppress fungal infections in human immunodeficiency virus (HIV)-infected individuals has contributed to a significant increase in C. krusei infection.3

Fluconazole is active against a variety of pathogens that cause systemic mycoses4 and is universally accepted as a triazole with unique pharmacokinetics with low molecular weight, good water solubility, weak protein binding, a long half-life, and a high level of cerebrospinal fluid penetration. It is well absorbed orally and has been effective in treating both superficial5 and systemic Candida infections5 and is the prophylactic drug of choice to prevent oropharyngeal6 and systemic candidosis8 in HIV-infected patients. Despite the initial claims of its efficacy in Candida infections in general, there are studies both in animals and humans that demonstrate the prophylactic and therapeutic failure of fluconazole against C. krusei.9,10

Immediately after the approval of its use in early 1990, fluconazole was used as a prophylactic antifungal in recipients of heart and bone marrow transplants.10,11 In one study conducted by Goodman et al.,10 patients receiving bone marrow transplants were randomly assigned to receive fluconazole (400 mg daily) or placebo. By the end of the treatment period, 28 patients of 177 in the placebo group developed systemic fungal infections, two of which were due to C. krusei. In comparison, five of 179 patients who received fluconazole developed systemic fungal infections, of which three were due to C. krusei. This study demonstrated that although fluconazole prevents infection with most pathogenic Candida species, it does not eradicate C. krusei.

In another retrospective study of 463 bone marrow transplant patients and leukaemias, there was a sevenfold greater incidence of blood stream or visceral infection with C. krusei in 84 patients who received fluconazole prophylaxis compared with the 355 patients who were receiving other modes of prophylaxis, including amphoteracin B, miconazole and ketoconazole, or no prophylaxis.9

There are several other reports that have documented the development of resistant strains of Candida after use of fluconazole as a prophylactic agent.
or as primary therapy for superficial candidosis. A study by Casanovas et al.11 also strongly supports these reports and suggests that flucanazole is not the ideal antifungal to prevent C. krusei infections. They observed significant (11%) C. krusei sepsicaemia in patients with neutropenia who received flucanazole. Goodman et al.12 also concluded that flucanazole can be effectively administered to reduce the incidence of systemic mycoses in severely immunosuppressed patients although they noted a tendency towards increased recovery of C. krusei during therapy and episodes of candidaemia due to the latter, in patients who received this drug. The foregoing strongly supports the view that the prophylactic use of flucanazole in compromised patients, while decreasing the frequency of C. albicans infections may promote the emergence of C. krusei.

One major reason for this phenomenon is likely to be the increased resistance of the yeast to azoles. A number of laboratory studies have reported higher minimum inhibitory concentrations (MIC) of flucanazole for C. krusei than for other species13-23 (range, 0.019-100 mg/mL for C. krusei compared with 0.019-20 mg/mL for C. albicans) although discordant correlations of in vitro testing and in vivo outcome have been observed.24 For the azole derivatives especially, the results of the in vitro susceptibility tests are profoundly affected by variables such as the methods and media used, endpoint definition, inoculum size, inoculum preparation, and the incubation conditions.25 Another key problem in interpreting antifungal susceptibility test results is the partial inhibition of growth with azoles. The in vitro activity of flucanazole against Candida species appear to be the hardest to determine meaningfully, being heavily dependent on the culture medium used to show the inhibitory activity.26 Hence, the available data need to be reviewed using a standardised assay method such as the NCCLS (National Committee for Clinical Laboratory Standards) reference method.27

Notwithstanding the above problems, there is an emerging consensus that C. krusei demonstrate a high level of resistance to flucanazole. Furthermore, the available data strongly suggest that flucanazole therapy (maintenance or intermittent), especially in low doses, as a prophylactic antifungal agent in compromised patients may result in the emergence of resistant C. krusei strains. Controlled clinical trials investigating the prophylactic and therapeutic use of triazoles, for either superficial or systemic candidoses, appear to be warranted prior to their widespread recommendation as a primary therapeutic agent. Finally, it should now be routine to identify Candida isolates to species level whenever flucanazole is instituted for the treatment of systemic mycoses.

References