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Editorial

Recurrent Vulvovaginal Infections by Resistant Fungi

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Introduction

Recurrent Vulvovaginal Fungal Infections (RVFI) are commonly caused by members of the genus *Candida*; the most prominent has been *C. albicans* (85-90%). However, there have been increasing reports finding non-albicans agents involved in such recurrences. These fungi are often resistant to the most commonly prescribed treatments. In addition, a combination of factors, including incorrect diagnosis of the fungus involved, off target accurate treatments and abuse of topical over-the-counter antifungals, have caused the selection of resistant strains with consequent perpetuation and/or recurrence of those infections [1].

The non-albicans most currently species identified include *C. glabrata*, *C. krusei*, *C. tropicalis*, and, in recent times, *C. dubliniensis* [1,2]. In rare cases also other fungal species could be involved, as previously reported with *Saccharomyces cerevisiae* and *Aspergillus* [3,4].

Prevalence

Candida species are known to colonize no less than 20% of all women of child bearing age and up to 30% of women with advanced pregnancy, as well as immunosuppressed [5]. Usually, non-albicans species are involved in less than 10% of all cases of RVFI.

The prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the USA was assessed with a survey involving more than 6,000 women older than 16 years of age by Foxman and his coauthors. He found that between 29% and 49% of the surveyed women reported a medically diagnosed fungal infection during their lifetime. Correspondingly, more than 20% of these women also recounted a one year recurrence of 4 or more of such infections. Therefore, he concluded that the cumulative probability of a first vaginal fungal infection was very high. Moreover, the probability of recurrence was 10% for women with 1 initial yeast infection by age 25, and 25% by age 50. His results were consistent across countries (France was the exception). He has attributed France's exception to variations in risk behavior, response to infection, or sampling biases [6].

Risk Factors

Numerous risk factors have been reported to intervene in RVFI. These include deficiencies at the local vaginal defense, gene

polymorphisms, allergic factors, serum glucose levels, antibiotic therapy, psychosocial stress and estrogens.

Additionally, it seems that post-menopausal patients who received a hysterectomy and suffer from RVFI seemed to be more predisposed to harbor more aggressive and resistant fungi [7].

Güzel recently reported having identified perineal lacerations and increased age (>50 years) to be predictors of finding *C. krusei* in vaginal samples of patients with RVFI [8].

According to Smeekens et al. it appears that genetic variation in the host plays a significant role regarding susceptibility to acquiring fungal infections. However, severe infections are linked to single gene immune-deficiency. The ones recently discovered include STAT1, STAT3 and CARD9. In contrast, immune system gene polymorphisms have been associated with recurrent vulvovaginal candidiasis [9].

Vaginal bacterial colonization was showed in a study by Ventolini et al. to be frequently concomitant (41.9%) with recurrent vulvovaginal fungal infections. The authors suggested a complete set of fungal and bacterial cultures when evaluating women with RVFI who failed to respond to antifungal therapy [10].

Diagnosis

Assessment of recurrent fungal vulvovaginitis should include a targeted history, skillful vulvar and vaginal examination as well as vaginal secretions pH determination, normal saline wet mount and 10% potassium hydroxide microscopy (by phase contrast at 400 x) preparation [1].

Classic symptoms include premenstrual itching, burning, redness from inflammation and non-odorous white cheese discharge at the vaginal introitus. Species identification, through fungal culture, is required to procure an accurate diagnosis in patients with RVFI [5,11].

Fungal culture results are usually available after 30 days. Therefore, efforts have been made to find a faster and reliable molecular method for *Candida* species. Recently, Diba et al. compared the standard morphological method of culture identification, to the molecular method of PCR - Restriction Fragment Length Polymorphism. They concluded that the 2 methods were comparable in identifying *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii* and *C. krusei* [12].

Treatment

The success rate for treatment of acute *C. albicans* vaginal candidiasis is approximately 80%. Differentiating *C. albicans* from non-albicans species has significant treatment consequences, since most C albicans infections can be effectively treated with a Fluconazole regimen, while many non-albicans species are resistance to it [5].

However, for patients with RVFI it has been suggested an initial

induction therapy, followed by a maintenance or suppression regimen to reduce relapse [5,11]. Weekly to monthly oral fluconazole has showed to suppress relapses, although therapy conclusion at 6 to 12 months has led to relapses in 50% of cases [13]. According to Donders et al. reducing 200 mg fluconazole maintained dose from 3 times a week to once monthly have more acceptable results [14].

Boric acid in gel capsules inserted vaginally is a reasonable first choice for non-albicans infections, including *C. krusei* as freshly reported by Guzel et al [8]. Additionally, they reported that all isolates were responsive to amphotericin B, caspofungin, ketoconazole, and miconazole. They also pointed out that they found a dose-dependent response and resistant rate for fluconazole of 42.9% and 57.1% respectively. Surprisingly, only 42.9% of the isolates were responsive to itraconazole and only 67.9% of them were responsive to voriconazole [8].

Tietz et al. described successful initial results in 14 patients of a new therapeutical regimen for *C. glabrata* that combined micafungin with topical ciclopiroxolamine [15]. Vaginal preparations containing polyenes, imidazole and ciclopiroxolamine or oral triazoles are all equally effective.

C. glabrata is resistant to the usual dosages of all local antimycotic. Therefore, vaginal boric acid suppositories or vaginal flucytosine are recommended, but flucytosine is not available in every country. Consequently, high doses of 800 mg fluconazole/day for 2-3 weeks are recommended [5].

Due to increasing resistance, oral posaconazole 2×400 mg/day plus local ciclopiroxolamine or nystatin for 15 days was proposed, since *C. krusei* is resistant to triazoles [8].

While considering therapy for RVFI it may also be necessary to think through alternative regimens for recalcitrant cases, until more targeted evidence based treatments become available.

Future

Future studies should include *Candida* auto-vaccination, antibodies against *Candida* virulence factors and other immunological trials. Probiotics should also be further evaluated.

Forthcoming developments and understanding of local genetic variation, susceptibility patterns and the role of biofilms of non albicans species might significantly contribute in the fight against RFVI.

Conclusions

Accurate diagnosis is the cornerstone for choosing an effective therapy for recurrent vulvovaginal infections by resistant fungi. Indiscriminate use of over the counter vaginal antifungal treatments unsupported by a precise diagnosis must be discouraged to avoid the insurgence of recurrent infections.

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