Candida autovaccination: A new strategy to prevent antifungal resistance?

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Dear Editor,

Recurrent vulvovaginal candidiasis (RVVC) is defined as four or more episodes of symptomatic vulvovaginal candidiasis (VVC) within one year (Kalaïarasan et al., 2017). VVC is an infection of the estrogenised vagina and the vestibulum, which can extend to the outside of the labia minora, the labia majora and the intercrural region (Mendling et al., 2012). In the range of 80–95%, *Candida albicans* is the most frequent yeast in chronically RVVC, with small regional differences (Mendling et al., 2012). *Candida albicans* is able to form blastospores, pseudomycelia, true mycelia and chlamydospores. *Candida glabrata*, which forms only blastospores, *C. krusei*, *C. guilliermondii*, *C. tropicalis*, *C. parapsilosis* and others can cause a vulvovaginitis with typical symptoms (Mendling et al., 2012).

VVC is a common public health problem of women presenting with a complaint of abnormal vaginal discharge (Kalaïarasan et al., 2017). In vitro susceptibility testing for fluconazole by the former National Committee for Clinical Laboratory Standards (NCCLS), now the Clinical Laboratory Standards Institute (CLSI), revealed that 21.1% of vaginal isolates were resistant to fluconazole (Bauters et al., 2002).

The increased resistance against fluconazole was observed in other studies, especially if the isolation of *C. glabrata* and *C. krusei* was prevalent (Kalaïarasan et al., 2017). For this reason, antifungal susceptibility testing plays an important role in the treatment of VVC, because RVVC is often difficult to treat (Kalaïarasan et al., 2017).

Host-related risk factors are significantly associated with VVC and RVVC, and include antibiotic use, uncontrolled diabetes, conditions with high reproductive hormone levels and genetic predispositions. Antibiotics alter the bacterial microflora of the vaginal and gastrointestinal tracts and thus allow for overgrowth of *Candida* spp. After antibiotic use, the increase in vaginal colonisation with *Candida* spp., mostly *C. albicans*, is estimated to be in the range of 10–30%, and VVC occurs in 28–33% of cases (Bauters et al., 2002). The increased antifungal resistance of non-*C. albicans* species and the considerable higher

frequency of non-*C. albicans* species in some countries is still unclear: genetic, immune-based, behavioral and nutritional factors have been taken into consideration (Bauters et al., 2002; Chowdhary et al., 2016; Ricchi et al., 2016; Stilo et al., 2016).

A lot of open questions remain in regard to the treatment of *Candida* vaginitis and new strategies have been tested to prevent it.

The standard treatment for VVC is the use of antimycotics. A possible and recently introduced alternative treatment of VVC is the use of specific autovaccines. Autovaccine therapy has a long medical history, although forgotten because of other efficient antimicrobial therapies. Autovaccines or autogenous vaccines are prepared from microorganisms harbored by the patient (Rusch and Schwiertz, 2007).

Rusch et al. (2007) reported that autovaccines were able to modulate the release of three potent immunoregulatory cytokines (IFN- γ , granulocyte-macrophage-colony stimulating factor, IL-1 β) without inducing a specific protection.

Lanzafame (2011) describes accurately the technique of autovaccine preparation: vaginal discharge should be cultured in agar Sabouraud and the identified colonies should be isolated and then subcultured in Trypticase Soy Agar. After 48 h at 37 °C, the surface medium should be scraped by calibrated plastic loop and the spherules washed three times with saline solution and resuspended in saline solution with opacity of 1 McFarland. The solution obtained should be heated at 70 °C in a water bath for 1 h for three days and tested for sterility. The spherules killed should be

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separated in four vials of 2 mL at the same concentration of fungi; the vials, then, should be injected in the deltoid of the patients (Lanzafame, 2011).

Rusch et al. (2007), in their study, collected vaginal samples from ten patients diagnosed with VVC. The treatment period with autovaccine was eight weeks. Nine out of the ten women showed an improvement of symptoms and clinical findings. Two of the ten women were tested positive for *Candida spp.* However, only one reported the symptoms to persist.

Lanzafame (2011), in his study, enrolled 74 women (suffering from at least four vaginitis episodes/year for at least two years) who underwent treatment with an autogenous vaccine. Symptomatology disappeared in 62 of the patients and six reported a relevant improvement. Laboratory follow-up showed absence of *Candida* in the vaginal secretion of 64/68 women who reported recovery or improvement (Lanzafame, 2011).

These studies show that *Candida* autovaccines may be a potent alternative in the treatment and prevention of vulvovaginal *Candida* infections. However, as Lanzafame (2011) reported in his study, in the first year after the end of the treatment relapses occurred in 23 (31%) patients, although with symptoms of a lesser intensity, and in 17 of them the infection resolved without antifungal treatment.

An important limit of our study is the low quality of the articles that we analyzed (JADAD Score < 3 for both) and the lack of information about the reduction of antifungal resistance. We therefore encourage other colleagues to conduct further investigations with a higher number of participants and with a control group in order to have a clearer idea of the real efficacy of this alternative treatment. This treatment could have also medico-legal implications, reducing the possibility of nosocomial infection in immunocompromised patients for whom even a *Candida* infection may have bad outcomes. Moreover, the collateral effects, represented only by a muscular pain in the sites of injections for 2–3 days after (Lanzafame, 2011), make this treatment well accepted and tolerated. A demonstrated

efficacy could lead, in future, to a diminished antifungal use and could represent an important tool to limit the drug resistance.

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