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ORIGINAL ARTICLE/ARTICLE ORIGINAL

In vitro susceptibility profile of 200 recent clinical isolates of *Candida* spp. to topical antifungal treatments of vulvovaginal candidiasis, the imidazoles and nystatin agents

Étude de la sensibilité in vitro de 200 isolats cliniques de Candida *sp. aux antifongiques locaux utilisés dans le traitement des candidoses vulvovaginales : les imidazolés et la nystatine*

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Vulvovaginal candidiasis;
Candida spp.;
Topical imidazole agents;
Nystatin;
Minimal inhibitory concentration;
Broth microdilution

Summary
Objective. — Topical antifungal treatment of vulvovaginal candidiasis is widely recommended. The most commonly recommended topical antifungals (the imidazoles clotrimazole, miconazole and econazole and the polyene nystatin) have been on the market for more than 30 years. There are only a few recent data available on the susceptibility of different *Candida* species to these antifungals, especially of non-*albicans Candida* species which appear to be less responsive to treatment with imidazoles. The study aimed to determine the *in vitro* susceptibility profile of a large number of recent clinical isolates of *Candida* spp. to the most commonly recommended topical antifungals.
Materials and methods. — An antifungal susceptibility test was performed according to the CLSI M27-A3 broth microdilution method, and minimal inhibitory concentrations were determined for econazole, miconazole, clotrimazole and nystatin.
Results. — The clinical isolates comprised of: 113 *Candida albicans*, 54 *Candida glabrata*, 11 *Candida krusei*, 11 *Candida tropicalis* and 11 *Candida parapsilosis*. The three azoles agents

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exhibited MIC_{90} values of 0.06 mg/L against *C. albicans* isolates, while nystatin exhibited a MIC_{90} of 4 mg/L. For non-*albicans Candida* isolates, MIC_{90} values ranged from 0.5 to 8 mg/L, from 1 to 4 mg/L and from 0.12 to 4 mg/L, for econazole, miconazole, clotrimazole, respectively. Nystatin MIC_{90} remained at 4 mg/L for all non-*albicans Candida* species tested.
Conclusion. — These results confirmed the susceptibility of *C. albicans* to the most frequently used topical agents and may support the use of alternative agents to imidazoles, such as nystatin, to treat vulvovaginal candidiasis caused by non-*albicans Candida* species.

MOTS CLÉS
Candidose vulvovaginale ;
Candida sp. ;
Imidazolés topiques ;
Nystatine ;
Concentration minimale inhibitrice ;
Microdilution

Résumé
Objectif. — Les antifongiques locaux sont largement préconisés en traitement des candidoses vulvovaginales. Peu d'études évaluent la sensibilité des *Candida* aux antifongiques les plus couramment utilisés et disponibles sur le marché depuis plus de 30 ans (clotrimazole, miconazole, éconazole, nystatine) ; en particulier, celle des *Candida* non-*albicans* qui semble plus réduite pour les imidazolés. Cette étude vise à déterminer le profil de sensibilité in vitro d'un large panel d'isolats cliniques récents de *Candida* sp. aux antifongiques locaux les plus répandus.
Matériel et méthodes. — La sensibilité des souches de *Candida* a été testée par la détermination des concentrations minimales inhibitrices de l'éconazole, du miconazole, du clotrimazole et de la nystatine en utilisant la technique de microdilution CLSI, M27-A3.
Résultats. — Le panel de 200 isolats comprend 113 souches de *Candida albicans*, 54 de *Candida glabrata* et 11 de *Candida krusei*, de *Candida tropicalis* et de *Candida parapsilosis*. Pour *C. albicans*, la CMI_{90} des trois azolés est de 0,06 mg/L ; celle de la nystatine est de 4 mg/L. Concernant les *Candida* non-*albicans*, les CMI_{90} des azolés varient de 0,5 à 8 mg/L pour l'éconazole, de 1 à 4 mg/L pour le miconazole et de 0,12 à 4 mg/L pour le clotrimazole. La CMI_{90} de la nystatine reste de 4 mg/L pour toutes les souches de *Candida* non-*albicans* testées.
Conclusion. — Cette étude confirme la sensibilité des *C. albicans* aux antifongiques locaux les plus couramment utilisés et suggère, qu'en substitution des imidazolés, la nystatine peut être proposée en traitement des candidoses vulvovaginales à *Candida* non-*albicans*.

Introduction

Vulvovaginal candidiasis (VVC) is the second most common cause of vaginitis after bacterial vaginosis, affecting millions of women worldwide every year [12,25]. This infection concerns 70% to 75% of women of all ages, at least once, and 40% to 45% of women will experience two or more episodes during their live [7,25].

VVC is caused by *Candida albicans* in 85% to 95% of cases [25], and by non-*albicans Candida* species, especially *C. glabrata*, in the remaining cases [4,18].

According to some studies, VVC infections due to non-*albicans Candida* species have become more common [6,29,30]. This rising incidence could be due to different reasons, including the excessive use of over-the-counter antifungal agents, single dose treatments, low dosage azole maintenance regimens [22] or the increased number of high-risk patients (e.g. diabetics and HIV women) [7,29]. However, other studies failed to confirm the increasing emergence of VVC caused by non-*albicans Candida* species [26,28].

VVC can be classified either as uncomplicated (approximately 90% of the cases) or complicated (approximately 10% of the cases) on the basis of clinical presentation, microbiological findings, host factors and response to therapy [7]. Uncomplicated VVC is usually due to *C. albicans* and it is treated with a variety of topical or oral antifungals, including nystatin and azoles. Azole agents, which are available as intravaginal (imidazoles) or oral formulations, are often recommended as a first-line treatment [7,17,31]. Several studies have shown that more than 90% of uncomplicated VVC can be successfully treated with either a single-dose of oral azole or a short-course topical imidazole therapy [17,23,31]. There are no data showing the superiority of a particular topical agent formulation or regimen over another [19,24].

Complicated VVC is defined as a severe or recurrent infection, or infection due to *Candida* species other than *C. albicans*, and/or as a VVC in an abnormal host (e.g. uncontrolled diabetes, debilitation or immunosuppression) [7]. The optimal treatment of complicated VVC remains unknown. However, complicated VVC is usually treated with multiple doses of oral azole or with a long-course topical imidazole therapy [17]. Several studies have shown that complicated non-*albicans* VVC infections are difficult to treat with imidazole agents, due to a reduced susceptibility of these species to this class of antifungal agent [10,14,16,21,22]. The polyenic agent nystatin has been proposed as an alternative to imidazoles for the treatment of complicated non-*albicans* VVC. Nystatin is known to be highly effective for the treatment of *Candida* infections and it is recommended in the European guidelines as a first-line treatment of chronic *C. glabrata* VVC [23].

The most commonly recommended topical antifungal agents for the treatment of VVC are the imidazoles clotri-