

# Persistent vulvovaginal candidiasis: systemic treatment with oral Fluconazole

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*Summary:* 52 patients affected by persistent vulvovaginal candidiasis underwent systemic therapy with oral Fluconazole at a dose of 150 mg once a week for 3 weeks. 31 (59.61%) patients were cured at the first control after therapy. Of the remaining 21 patients, 4 (7.69%) were lost at follow-up and 17 (32.69%) underwent a second cycle of systemic therapy with complete recovery confirmed at the further controls. The overall percentage of recoveries was equal to 92.30%. The results suggest that Fluconazole is very effective in mycotic vulvovaginitis with irrelevant side effects.

*Key words:* Vulva; Vagina; Candidiasis; Fluconazole.

## INTRODUCTION

The incidence of candidal vulvovaginitis (VVC) has increased from 118 per 100,000 to 200 per 100,000 in the last 10 years (<sup>1</sup>).

Evidence shows that 75% of women will have at least one episode of VVC during their child-bearing years, and that approximately 40-50% will experience a second episode in their life-time (<sup>2, 3</sup>).

A small subpopulation of undetermined size, probably less than 5% of adult women, has recurrent, often untractable episodes of this disorder.

The rarity of *Candida* isolation in girls before menarche and the lower prevalence of candidal vaginitis after menopause em-

phasizes the hormonal dependence of this infection (<sup>2, 3</sup>).

Mycotic disease in humans and animals is an accidental event in the cycle of all pathogenic mycetes, both saprophyte and parasite, and although the natural history of this disease is still unknown, an important role is played by predisposing factors that can explain, at least in part, its frequent recurrence (<sup>4</sup>).

Some socio-cultural aspects should be taken into proper consideration: in fact, drug use, synthetic garments, and freedom in sexual habits accompany the mycotic infection due to both general endogenous factors, such as metabolic diseases, immune deficiencies, dysendocrinisms etc., and to iatrogenic causes such as the use of antibiotics, corticosteroids, etc.

An important role is also played by local imbalances of the vaginal ecosystem, which are linked to alterations of the vaginal flora.

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In fact, vaginal flora is principal defence against candidal colonizations<sup>(5)</sup>.

Once it reaches the vagina, predominantly from the adjacent perianal area<sup>(6)</sup>, to become pathogenic, the microorganism has to adhere to the epithelial cells on which it grows and from where it invades the adjacent cells; these phenomena are counteracted or hampered by the resident lactobacillar flora responsible for nutritive substrates and *Candida* receptors.

Equally remarkable is the role of the source of infection in the pathogenesis and especially in its recurrence.

Since it is also a sexually-transmitted disease, particular importance has been attributed to male colonization which is recorded anyway in the genesis of recurrence in no more than 30-40% of cases<sup>(7, 8)</sup>.

The possibility of reinfection from intestinal reservoirs is one of the most common; furthermore, it is known that the possible principle reserve of the recurrence is the vagina itself, when a first ineffective treatment has failed to reach the deepest epithelial layers, where mycete can live and break out again after physiological cell shedding<sup>(9)</sup>.

The increased incidence of mycotic pathology in general, and of genital mycotic pathology in particular, has stimulated pharmacological research aimed at identifying and setting-up a selective treatment capable of bringing about eradication of the infection.

The topical treatments usually applied have shown to be barely effective due to poor execution, but are mainly due to incomplete sterilization of source and reinfection caused by the partner or from an extravaginal site<sup>(10)</sup>.

Particular interest is raised by the systemic use of active antimycotic drugs to reclaim the infection reservoirs and to resolve recurrence in a high percentage of cases.

The chemotherapeutic antimycotic agents which are no longer manufactured because of their high toxicity and poor solubility, were exclusively employed in topical treatments<sup>(11, 12)</sup>.

Fluconazole (a triazolic agents), on the other hand, is a powerful specific inhibitor of the synthesis of mycotic sterols.

Because of its pharmacological and pharma-dynamic characteristics, it is well-tolerated orally; its bioavailability amounts to 90% with peaks of plasmatic concentration ranging between 30 and 90 minutes after administration, and its plasmatic half-life is about 30 hours, which supports the treatment of vaginal *Candidiadis* by "short therapy".

The drug induces plasmatic levels sufficient to eliminate the infection reserves<sup>(13)</sup>.

In our study we intended to test efficacy and tolerance of Fluconazole in the systemic treatment via os of persistent vulvovaginal *Candidiadis* on the basis of the following considerations: the ubiquitous character of the mycotic localization, frequent recurrence related to an incomplete topical sterilization of the vaginal source, sexual and extragenital infections, proven selectivity of Fluconazole while respecting the vaginal and intestinal ecosystem, and finally, the possibility of adopting the same therapy for the partner.

## MATERIALS AND METHODS

At the Colposcopic and Cervico-vaginal Pathology and Laser Surgery Unit of the II Clinic of Obstetrics and Gynecology of the University of Rome, "La Sapienza", we studied 179 (22.09%) cases of vaginitis from *Candida albicans* out of a group of 810 patients who had come for a first visit to our clinic. The vaginitis was assessed cytologically and confirmed by microbiological culture.

Age of patients ranged between 16 and 55 years (mean = 27).

All patients presented the classical symptoms of the infection: pruritus, burning, dyspareunia, dysuria, and in some cases pelvic aegae and contemporarily leukorrhea and flush of the external genitals.

All 179 patients underwent topic antimycotic therapy; the patients that showed persistence of the infection after 4 weeks from the end of treatment were selected for a systemic treatment with Fluconazole (Biozelene 150 mg, Bioindustria) at a dose of 150 mg once a week for three weeks consecutively.

Pregnant and HIV-seropositive patients were ruled out of the study.

The same therapy was prescribed for partners.

Follow-up consisted of a clinical colposcopic, cytological, and cultural control one month after the end of systemic treatment and then at three-monthly intervals.

The longest follow-up was 30 months, the shortest 16 months; the mean period was equal to 20 months.

## RESULTS

52 (29.05%) patients out of the 179 treated with topical therapy presented persistent pathology at one month from the end of treatment.

All 52 patients underwent systemic therapy with Fluconazole at a dose of 150 mg once a week for three weeks.

31 (59.61%) patients were cured at the first control after systemic treatment.

On the remaining 21 patients, 4 (7.69%) were lost at follow-up and 17 (32.69%) underwent a second cycle of systemic therapy with complete recovery confirmed at the further controls.

The overall percentage of recoveries was equal to 92.30% (Table 1).

Among the 48 patients, none described side effects such as to necessitate suspension of treatment.

Table 1. - Results of systemic treatment with Fluconazole in patients affected by persistent Candidal vulvo-vaginitis.

	Complete response		Persistence		No. follow-up	
	No.	%	No.	%	No.	%
I Treatment	31	59.61	21	40.39	-	-
II Treatment	17	32.69	-	-	4	7.69
Total Complete response	48	92.30				

By the end of therapy, the complete remission of symptoms was observed in all patients.

## DISCUSSION

The mechanisms that permit the transformation of vaginal asymptomatic colonization into a candida vulvovaginitis are complex. Symptomatic vaginitis develops in the presence of factors that increase the virulence of Candida and/or reduces local defences, thus altering the delicate balance between Candida and local protective bacterial flora, which is probably the most important defensive mechanism<sup>(6)</sup>.

For patients affected by persistent infection, it is not always possible to isolate a precipitant factor; however, for these patients it is desirable to avoid the use of antibiotics, especially those with a wide spectrum, oral contraceptives, synthetic garments, and hormonal therapies. Furthermore, it is necessary to assess tolerance to glucose and to rule out other systemic pathologies that could account for the persistence of the infection.

Also, although rarely, it is possible that the patients who do not react to conventional therapies present infrequent organisms resistant to standard drugs.

However, recurrences after topic treatment necessitate a different therapeutical approach capable of acting systemically.

Although systemic treatment is far more expensive compared to topic therapy, nonetheless, it should be evaluated for its therapeutical efficacy, for its psychological relief to the patient affected by this pathology, and for its clinical validity. Data analysis shows that Fluconazole is a drug highly selective and remarkably effective in mycotic phlogosis with regard to both the regression of clinical symptoms and to the negativity of cyto-cultural exams at the end of therapy.

The irrelevant side effects, at the doses and conditions applied, together with a

good compliance by both patient and partner, suggest that not only is the systemic administration an alternative to topical treatment, but that it is also an adequate tool for the eradication of the infection and the reclaiming of the reservoirs while respecting the ecologic balance of the vaginal ecosystem.

It is clear that, although the persistence of the infection can be linked to general predisposing factors, much of this pathology is connected with local vaginal mechanisms, and for this reason it could be useful to assess whether a microbial lactobacillar supplement, already indicated<sup>(14)</sup>, can prevent a recurrent infection.

Therefore, further studies are necessary for a deeper comprehension of the biological mechanisms responsible for the virulence of the mycete, so as to produce drugs capable of interfering also in the modulation of the immune system, as well as to set up both therapeutical and preventive measures.

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#### REFERENCES

- 1) Odds F.C.: "Candidosis of the genitalia". In: Odds F.C., ed. 'Candida and Candidosis', 2nd ed. London, Balliere Tindall, 1988, 124.
- 2) Sobel J.D.: "Candidal Vulvovaginitis". *Clin. Obst. Gyn.*, 1993, 36, 1.

- 3) O'Conner M.I., Sobel J.D.: "Epidemiology of recurrent vulvovaginal candidiasis: identification and strain differentiation of *Candida albicans*". *J. Infect Dis.*, 1986, 154, 358.
- 4) Spinillo A.: "Recurrent vaginal Candidiasis". *J. Reprod. Med.*, 1992, 37, 343.
- 5) Sobel J.D.: "Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis". *Am. J. Obst. Gyn.*, 1985, 152, 924.
- 6) Auger P., Joly J.: "Microbial flora associated with *Candida albicans* vulvo-vaginitis". *Obst. Gyn.*, 1980, 55, 397.
- 7) Odds F.C.: "Genital candidosis". *Clin. Exper. Dermatol.*, 1982, 7, 345.
- 8) Horowitz M.R., Edelstein S.W., Lippman L.: "Sexual transmission of *Candida*". *JAMA*, 1987, 69, 883.
- 9) Miles J.D., Olsen L., Rogers A.: "Recurrent vaginal candidosis. Importance of intestinal reservoir". *JAMA*, 1977, 238, 1836.
- 10) Dennerstein G.: "Management of recurrent vaginitis". *Drugs*, 1981, 21, 231.
- 11) Osser S., Haglund A., Westrom L.: "Treatment of Candidal vaginitis". *Acta Obst. Gyn. Scand.*, 1991, 70, 73.
- 12) Maccato M.L., Raymond H.K.: "Fungal vulvovaginitis". *Current Opinion Obst. Gyn.*, 1991, 3, 849.
- 13) Sobel J.D.: "Fluconazole maintenance therapy in recurrent vulvovaginal candidosis". *Int. J. Obst. Gyn.*, 1992, 37 (Suppl. 1), 17.
- 14) Hilton E., Isenberg H.D., Alperstein P., France K., Borenstein M.T.: "Ingestion of yogurt containing *Lactobacillus acidophilus* as a prophylaxis for candidal vaginitis". *Ann. Intern. Med.*, 1992, 116, 353.

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