

Successful Treatment of Refractory Recurrent Vaginal Candidiasis with Cetirizine Plus Fluconazole

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■ Abstract

Objective. To determine the prevalence of allergy in patients with recurrent vaginal candidiasis (RVC) and the efficacy of fluconazole in combination with an antihistamine drug in RVC patients who do not respond to fluconazole alone.

Materials and Methods. Participants in the study included 24 women with RVC. All subjects filled out an International Study of Asthma and Allergies in Childhood questionnaire and 23 performed skin prick tests for immediate type 1 hypersensitivity as part of atopy assessment. All subjects were treated with fluconazole 150 mg weekly and were followed every 2 months for 6 months. Those who did not respond to fluconazole alone received cetirizine 10 mg daily in addition to the antifungal medication and were followed up for 6 months.

Results. The majority of women had a history of allergy (60%) and 10 of them (43%) had at least 1 positive result of a skin prick test to aeroallergens. Nineteen patients (79%) responded to fluconazole alone. The 5 patients who remained with symptoms had a medical history of allergy and obtained remission when cetirizine was associated with fluconazole.

Conclusions. Patients with RVC refractory to standard antifungal therapy and a history of allergy may respond to the combination of antihistamine and antifungal therapy. ■

Key Words: Recurrent vaginal candidiasis, fluconazole, allergy, antihistamine, skin prick test

Recurrent vaginal candidiasis (RVC) is an opportunistic mucosal infection that affects up to 5% of otherwise healthy women of childbearing age [1, 2]. The disease is caused by several *Candida* species [3], but *Candida albicans* is the causative agent in approximately 85% to 90% of symptomatic, culture positive RVC patients [4–7]. Antimycotic agents, although effective in eradicating individual attacks, do not cure RVC in the majority of women. Antifungal drug resistance does not appear to contribute to RVC [8, 9]. Women have sporadic vaginal candidiasis precipitated by pregnancy, oral contraceptives, uncontrolled diabetes mellitus, and antibiotics. All of these factors could also cause RVC; however, many women with RVC have idiopathic RVC. Often the exogenous predisposing factors for RVC cannot be recognized [7, 8, 10]. RVC is presumed to result from diminished host defense mechanisms that increase susceptibility to symptomatic infection. Accordingly, it is postulated that the conversion of *C. albicans* from a vaginal commensally infection to a pathogen results from abnormalities in systemic cell-mediated immunity [11–14]. A similar process is thought to be associated with chronic mucocutaneous candidiasis [15, 16]. Allergy may also play a role in RVC. A few reports have documented allergy in patients with RVC and high levels

This study was supported by NIH grant AI-30639. Dr. Edgar M. Carvalho is senior investigator of the Brazilian National Research Council (CNPq).

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of *C. albicans*-specific IgE have been documented in vaginal washes [17, 18]. Moreover, some symptoms observed in RVC, such as pruritus and burning, may be related to allergy.

This study evaluated the effect of an antifungal agent used to decrease the number of microorganisms in the vagina, in combination with an antihistamine used to decrease the allergic symptoms in RVC patients who do not respond to antifungal drugs alone.

MATERIALS AND METHODS

Twenty-seven women with RVC participated in this case series. The study followed all guidelines of the institutional ethics committee and informed consent was obtained from all patients. The majority of women were using some contraceptive method and were referred to the gynecology service of the Hospital Universitário Prof. Edgard Santos from the Federal University of Bahia because of a history of at least four episodes of candidal vaginitis during the last 12 months. Episodes were not correlated with menstrual cycle. Swab specimens were placed on Sabouraud's dextrose agar and subsequently identified at the species level with the use of the API 20C system (BioMerieux, Marcy L'Etoile, France). We did bacterioscopy to exclude others pathogens. All patients had positive *C. albicans* vaginal cultures at the beginning of the treatment. None had diabetes mellitus, anemia, AIDS, autoimmune or thyroid diseases, or used immunosuppressive drugs. We used standard medical histories to assess symptoms, the frequency and intensity of RVC episodes, triggering factors, and individual and familial allergy history. Moreover, all subjects filled out an International Study of Asthma and Allergies in Childhood questionnaire [19].

The women underwent physical examinations and skin prick tests for allergy and were treated with fluconazole 150 mg once weekly. All the patients were culture positive and were symptomatic when fluconazole therapy was initiated. The patients were followed up every 2 months for 6 months. On each visit they were asked about their symptoms and vaginal material was obtained for culture. We considered a therapeutic response when no symptoms or signs of candidiasis were referred or detected respectively at each visit. Patients who did not respond to fluconazole after 2 months of therapy received cetirizine 10 mg daily associated with fluconazole.

Atopic status was defined as the presence of a history of allergic respiratory disease in the preceding 12 months,

as well as a positive skin prick test result for at least 1 antigen tested.

Skin Prick Test for Immediate Hypersensitivity

The skin prick test for immediate hypersensitivity was performed on the right forearms of all individuals using a panel with 7 relevant local allergens: *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, Pool of Molds I (*Alternaria alternata*, *Cladosporium herbarum*, and *Chaetomium globosum*), Pool of Molds II (*Mucor mucedo*, *Pullularia pullulans*), *Candida albicans*, dog and cat epithelia (Alk Abello; Denmark) according standardized procedure [20]. Histamine (1/1,000) and saline were used as positive and negative controls, respectively. The size of the reaction was determined by measuring the greatest transverse diameter of the papulae after 15 minutes of antigen implantation. The skin reaction was considered positive when the diameter was >3 mm in the presence of a positive histamine reaction and in the absence of a reaction to saline control.

RESULTS

Of the 27 women, 24 completed the study protocol and therefore had full data available for analysis. All had positive cultures for *C. albicans*. The mean age was 32 years and the mean illness duration was 3 years. Data related to previous history of allergy, familiar history of allergy, and the frequency of positive immediate skin test results are shown in Table 1. Sixteen of 24 (66%) women had a personal history suggestive of atopy. The number of patients with at least 1 positive skin test result was 10 (43%), and all of them had personal and family history of allergy.

Nineteen of the 24 patients (79%) responded to treatment with fluconazole alone. These patients had no symptoms at the first follow-up visit (after 2 months), but 5 of them remained with positive cultures. However, 5 patients still had the same symptoms after 2 months therapy with fluconazole and had a positive culture for *C. albicans*. They reported pruritus and burning, with no total improvement. These patients were then

Table 1. History of Allergy and Skin Prick Test Response to Aeroallergens in Patients with Recurrent Vaginal Candidiasis

Variables	No. of patients (%)
Family history of allergy	14/24 (58.3)
Personal history of allergy	16/24 (66.6)
Positive skin-prick test results	10/24 (43)

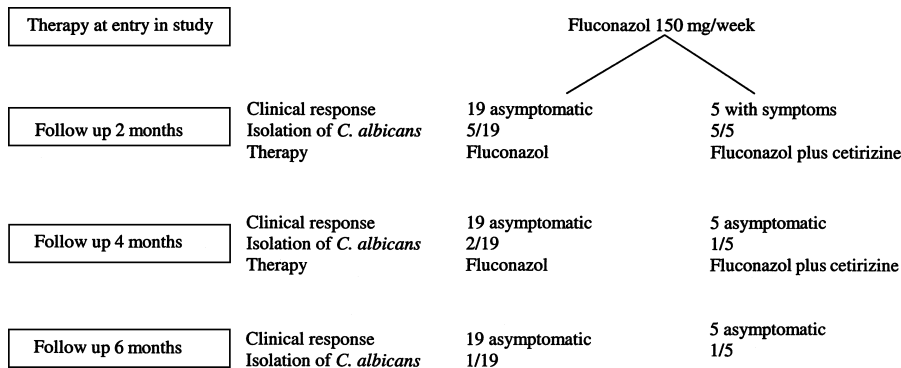


Figure 1. Clinical response and isolation of *C. albicans* in 24 patients with RVC treated initially with fluconazole alone and those who failed, with fluconazole plus cetirizine.

treated with the antihistamine (cetirizine) in addition to fluconazole (Figure 1). All 5 patients had individual and familiar history of allergy and experienced intensive symptoms (pruritus and burning) at the initial therapy; 2 of them had positive skin prick test to aeroallergens result. In 2 patients the test results were negative, and 1 patient did not take the test. After 2 months of the combination treatment (fluconazole + cetirizine), these 5 patients were free of symptoms, but 1 still had a positive culture for *C. albicans*. At 6 months, all 24 patients remained free of symptoms or signs of vaginal candidiasis. Two patients, 1 in the fluconazole group and 1 in the group that received combined therapy, still had *C. albicans* in their vaginal fluid.

DISCUSSION

It is now accepted that RVC can be managed and sometimes cured by long-term maintenance therapy with topical or systemic antifungal drugs. Several possible regimens have been used to treat RVC, such as ketoconazole 100 mg daily for 6 months [21], itraconazole 50 to 100 mg daily for 6 months [22], fluconazole 100 mg once a week for 6 months [23], and clotrimazole 500 mg vaginal suppositories weekly [21]. Sobel [21] showed that during maintenance therapy with ketoconazole 100 mg daily, which should last for at least 6 months, 90% of patients were protected from symptomatic recurrences. Similarly, a large multicenter study using 150 mg oral fluconazole once monthly demonstrated 50% reduction in the recurrence rate of symptomatic RVC [24]. The pharmacokinetic properties of fluconazole favor its use in maintenance treatments regimens. Therapeutic tissue concentrations are sustained for 72–96 hours after an oral dose, and concentrations remain sufficient to prevent fungal growth and germ tube formation for an additional several days [25, 26]. However therapeutic failure may

occur and a small percentage of women may require maintenance azole regimens for several years [27].

The immunopathogenesis of RVC is not completely understood. Impairment of type 1 immune response is observed in these patients and may prevent an effective defensive mechanism against *C. albicans* [28, 29]. More recently, evidence has accumulated that allergy may play a role in RVC. Both IgE antibody and anti-*C. albicans* have been documented in patients with RVC [18], and there is a strong association between allergy and RVC [30]. Moreover, some symptoms observed in RVC, such as burning and pruritus, are common in allergic reactions. Therefore, allergy is considered an important factor in both the pathogenesis and symptoms of RVC [31, 32]. In the present study, 5 patients who failed to respond to fluconazole were treated with fluconazole plus cetirizine. All of these women had history of allergy and became asymptomatic after combining antihistamine and antifungal therapy. In such case, it is likely that a histamine release may not only contribute to symptoms, but also may suppress cell-mediated immune responses by production of prostaglandin E₂. The antihistaminic drugs could be acting on both levels, controlling the signs and symptoms and decreasing a persistent allergic response, thereby contributing to the development of an effective immune response.

The results of this study indicate that an antihistamine drug should be combined with antifungal therapy in patients with RVC who have history of allergy and who fail to respond to therapy with antifungal drugs alone.

REFERENCES

1. Sobel JD. Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 1985;152: 924–35.
2. Hurley R. Recurrent *Candida* infection. *Clin Obstet Gynecol* 1981;8:209–14.

3. Sobel JD. Pathogenesis and epidemiology of vulvovaginal candidiasis. *Ann N Y Acad Sci* 1988;544:547-57.
4. Fleury FJ. Adult vaginitis. *Clin Obstet Gynecol* 1981;24:407-38.
5. Morton RS, Rashid S. Candidal vaginitis: natural history, predisposing factors and prevention. *Proc R Soc Med* 1977;70:3-12.
6. Spinillo A, Pizzoli G, Colonna L, Nicola S, De Seta F, Guaschino S. Epidemiologic characteristics of women with idiopathic recurrent vulvovaginal candidiasis. *Obstet Gynecol* 1993;81:721-7.
7. Sobel JD. Vaginitis. *N Engl J Med* 1997;337:1896-903.
8. MacNeill C, Weisz J, Carey JC. Clinical resistance of recurrent *Candida albicans* vulvovaginitis fluconazole in the presence and absence of in vitro resistance. *J Reprod Med* 2003;48:63-8.
9. Fong IW, Bannatyne RM, Wong P. Lack of in vitro resistance of *Candida albicans* to ketoconazole, itraconazole and clotrimazole in women treated for recurrent vaginal candidiasis. *Genitourin Med* 1993;69:44-6.
10. Fidel PL, Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. *Clin Microbiol Rev* 1996;9:335-48.
11. Syverson RE, Buckley H, Gibian J, Ryan GM. Cellular and humoral immune status in women with chronic *Candida* vaginitis. *Am J Obstet Gynecol* 1979;134:624-7.
12. Fong IW, McCleary P, Read S. Cellular immunity of patients with recurrent or refractory vulvovaginal moniliasis. *Am J Obstet Gynecol* 1992;166:887-90.
13. Corrigan EM, Clancy RL, Dunkley ML, Evers FM, Beagley KW. Cellular immunity in recurrent vulvovaginal candidiasis. *Clin Exp Immunol* 1998;111:574-8.
14. Witkin SS. Inhibition of *Candida*-induced lymphocyte proliferation by antibody to *Candida albicans*. *Obstet Gynecol* 1986;68:696-9.
15. Lilic D, Cant AJ, Abiunun M, Calvert JE, Spickett GP. Chronic mucocutaneous candidiasis. *Clin Exp Immunol* 1996;105:205-12.
16. Kirkpatrick C. Chronic mucocutaneous candidiasis. *Eur J Clin Microbiol Infect Dis* 1989;8:448-56.
17. Witkin SS, Jeremias J, Ledger WJ. Vaginal eosinophils and IgE antibodies to *Candida albicans* in women with recurrent vaginitis. *J Med Vet Mycol* 1989;27:57-8.
18. Witkin SS, Jeremias J, Ledger WJ. A localized vaginal allergic response in women with recurrent vaginitis. *J Allergy Clin Immunol* 1988;81:412-6.
19. Beasley R. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema: ISAAC. *Lancet* 1998;351:1225-32.
20. Middleton E Jr, Reed CE, Ellis EF, Adkinson Jr NF, Yunginger JW, Busse WW, eds. *Allergy Principles and Practice*, 5th ed. Mosby; 1998:430-7.
21. Sobel JD. Recurrent vulvovaginal candidiasis: a prospective study of the efficacy of maintenance ketoconazole therapy. *N Engl J Med* 1986;315:1455-8.
22. Van Heusden AM, Merkus JM. Chronic recurrent vaginal candidosis: easy to treat, difficult to cure. Results of intermittent treatment with a new oral antifungant. *Eur J Obstet Gynecol and Reprod Biol* 1990;35:75-83.
23. Sobel JD. Treatment of recurrent vulvovaginal candidiasis with maintenance fluconazole. *Int J Gynaecol Obstet* 1992;37:17-34.
24. Sobel JD. Recurrent *Candida* vaginitis: a rational approach to therapy. *Drug Ther* 1982;12:41-55.
25. Dellenbach P. Penetration of fluconazole into vaginal tissues and secretions. In: Richardson RG, ed. *Fluconazole and its Role in Vaginal Candidiasis*. Royal Society of Medicine Services; 1989:19-24.
26. Houang ET, Chappatte O, Byrne D, Macrae PV, Thorpe JE. Fluconazole levels in plasma and vaginal secretion of patients after a 150 mg single oral dose and rate of eradication of infection in vaginal candidiasis. *Antimicrob Agents Chemother* 1990;34:909.
27. Sobel JD. Management of patients with recurrent vulvovaginal candidiasis. *Drugs* 2003;63(11):1059-66.
28. Carvalho LP, Bacellar O, Neves N, Jesus A, Carvalho E. Downregulation of IFN-gamma production in patients with recurrent vaginal candidiasis. *J Allergy Clin Immunol* 2002;109:102-5.
29. Witkin SS. Immunologic influencing susceptibility to recurrent candidal vaginitis. *Clin Obstet Gynecol* 1991;34:662-8.
30. Moraes PSA. Recurrent vaginal candidiasis and allergic rhinitis: a common association. *Ann Allergy Asthma Immunol* 1998;81:165-9.
31. Cenci E, Mencacci A, Del Sero G, Bistoni F, Romani L. Induction of protective Th1 response to *Candida albicans* by antifungal therapy alone or in combination with an interleukin-4 antagonist. *J Infectious Disease* 1997;176:217-26.
32. Rigg D, Miller MM, Metzger J. Recurrent allergic vulvovaginitis: treatment with *Candida albicans* allergen immunotherapy. *Am J Obstet Gynecol* 1990;162:332-36.