Drugs 2003; 63 (11): 1059-1066
0012-6667/03/0011-1059/$33.00/0

Management of Patients with Recurrent Vulvovaginal Candidiasis

Jack D. Sobel

Division of Infectious Diseases, Department of Internal Medicine, Wayne State University School of Medicine, Detroit, Michigan, USA

Contents

Abstract

Recurrent vulvovaginal candidiasis (RVVC) is by no means uncommon and is a source of considerable physical discomfort in addition to serving as a major therapeutic challenge. The syndrome is multifactorial in aetiology and hence management strategies must recognise the complex aetiological pathways. Many women receiving the misplaced diagnosis of RVVC have a variety of other infectious and non-infectious entities presenting with identical symptoms. Hence the first step in management is confirming the diagnosis of RVVC including microbial confirmation and species identification. Efforts should be made to identify and correct a causal mechanism. Maintenance suppressive azole antifungal regimens are highly effective in controlling symptoms, although cure is less common. Further advances in achieving higher cure rates await the availability of non-azole fungicidal agents.

1. Epidemiology

Recurrent vulvovaginal candidiasis (RVVC) can be defined as four or more attacks of symptomatic candidal vaginitis in a 12-month period.[1]

The true incidence of RVVC remains unknown. Estimates over many years suggest that the incidence is approximately 5% of women during their reproductive age. A recent study by Foxman et al., which included interviewing 2000 women, determined that the incidence of RVVC in the US is approximately 8% of women of reproductive age.[2] This almost certainly represents an overestimation. The availability of over the counter (OTC) antimycotic agents precludes any prospective data collection determining the incidence of candidal vaginitis in North America.

Women with a history of RVVC account for the vast majority of physician visits by women for VVC. The natural history of RVVC differs from that of sporadic, uncomplicated disease in that the latter variety of candidal vaginitis tends to decrease in frequency with age, decreasing from the maximal attack rate in women 15–30 years of age, with a progressive decrease over the next 2 decades. In contrast, women with RVVC continue to have attacks of symptomatic disease throughout the reproductive age with no progressive decline in attack frequency. The incidence of RVVC appears increased in women who are HIV positive as well as in a variety of other risk groups, including those with uncontrolled diabetes mellitus and women taking corticosteroids and other immunosuppressives.

2. Microbiology

The prevalence of *Candida* species responsible for RVVC does not differ substantially from that observed in women with uncomplicated, sporadic VVC.[3] In the latter, 90–95% of isolates obtained from women with uncomplicated VVC are caused by *Candida albicans*. Women with RVVC have a modest increase in the frequency of attacks caused by non-*albicans Candida* species reaching approximately 10–15%.[1,4] The second most common *Candida* species isolated from women with RVVC is *C. glabrata* at 5–10%.

3. Pathogenesis

It is simplistic to assume that RVVC is caused by a single mechanism. RVVC may be primary (idiopathic) or secondary to a variety of host or microbial factors. Host factors include uncontrolled diabetes, repeated exposure to antibacterials, immunosuppression caused by HIV and other diseases, such as systemic lupus erythematosus, as well as to a variety of immunosuppressive drugs, e.g. corticosteroids. Exogenous estrogens, in the form of oral contraceptives (OCs), hormone replacement therapy (HRT) or the local application of intravaginal oestrogen, all may be responsible for recurring episodes. Microbial factors responsible for RVVC include infection caused by non-*albicans Candida* species, which tend to be significantly less susceptible to azole agents and, rarely, RVVC may be due to resistant *C. albicans*.[5]

There are two phases critical in the development of candidal vaginitis. The first requires vaginal colonisation by *Candida* microorganisms. The second is the transformation from asymptomatic colonisation to symptomatic candidal vaginitis. There are distinct risk factors for colonisation, as well as for transformation from the asymptomatic to the symptomatic vaginitis phase. These risk factors are identified in figure 1. It is important to recognise that women prone to RVVC have a higher frequency of vaginal colonisation by *Candida* species. This may be recognised by both culture and polymerase chain reaction studies.[3]

The pathogenesis of idiopathic, or primary, RVVC is incompletely understood. Antifungal resistance as a cause of idiopathic RVVC due to *C. albicans* is extremely rare in these patients. The issue of relapsing disease as opposed to re-infection of the host has been debated for several decades. Evidence exists from typing studies, that repetitive isolates obtained on a longitudinal basis from the same patient tend to be identical, suggesting a relapsing, rather than a re-infection process.[6] The relapses indicate persistence of *Candida* microorganisms in the vagina or the gastrointestinal tract, and most recent studies suggest that the primary reservoir for relapsing candidal vaginitis is the lower genital tract, *per se*. While sexual transmission may be an important factor in some patients, in the majority of patients, a persistent vaginal reservoir is maintained without the need for re-infection from an infected partner.[1,4,7]

Studies in the 1970s suggested that idiopathic RVVC was the consequence of an acquired *Candida* antigen-specific host immunodeficiency with impaired systemic cell mediated immunity (CMI) directed at *Candida* antigen. This was based on a decreased *in vitro* lymphocyte response to *Candida* antigen, as well as skin tests performed on patients with RVVC which demonstrated *Candida* anergy. In the 1980s, however, repeated studies showed that the cutaneous anergy was the consequence and not

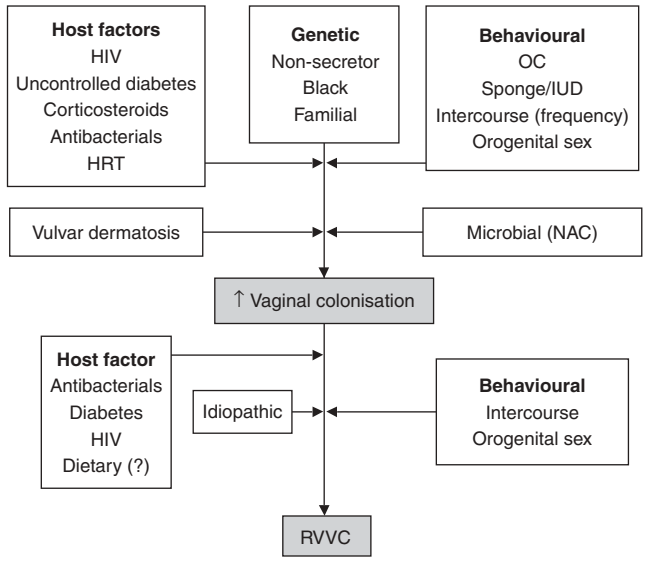

Fig. 1. Pathogenesis of recurrent vulvovaginal candidiasis (RVVC). **HRT** = hormone replacement therapy; **IUD** = intrauterine device; **NAC** = non-*albicans Candida* species; **OC** = oral contraceptive.

the cause of the infection.[8] Moreover, similar studies showed that patients with RVVC frequently demonstrated an immediate hypersensitivity reaction to *Candida* spp. that appeared within 20 minutes. Similarly, animal studies using the rodent model for experimental candidal vaginitis failed to show that reduced systemic CMI pre-disposed to candidal vaginitis.[8] These studies showed compartmentalisation of *Candida* immunity with separation of the anti-*Candida* mucosal immune response in the vagina from the systemic response.[8]

Women with RVVC do not experience recurrent cutaneous, oral or oesophageal candidiasis. More recent studies have indicated that patients with RVVC have normal lymphocyte proliferation and cytokine responses to a variety of *Candida* antigens.[8] Thus, if impairment in T-cell function exists in women with RVVC, it appears to be confined to the lower genital tract. Evidence exists that local immunoglobulins, specifically IgA and IgG, play a role in the protection of the lower genital tract from candidal infections. Women with RVVC have not been shown to have any reduction in vaginal antibody concentrations.

Accordingly, it has been hypothesised that women with idiopathic RVVC have an organ-specific, antigen-specific abnormality, whereby the normal host organism inter-reaction in the vagina is impaired.[8] It has been suggested that the normal protective T helper (Th)1 response is replaced by a Th2 immune response, whereby the normal tolerance demonstrated by the vaginal mucosa for *Candida* spp. colonisation is lost and re-exposure of the vagina to *Candida* antigen results in an immediate hypersensitivity reaction with the development of recurrent vulvovaginal symptoms including pruritus, oedema and erythema. In the majority of women with RVVC, most episodes of symptomatic vaginitis appear without any recognisable precipitating factors.

4. Clinical Manifestations

The clinical manifestations of RVVC are identical to symptomatic episodes seen in women with uncomplicated disease. Diagnosis of RVVC is similarly dependent on a combination of findings with normal pH, positive microscopy and culture. Confirmation of the diagnosis of candidal vaginitis in women with recurring episodes is to be emphasised. In practice, the majority of women receiving the diagnosis of RVVC do not, in fact, have recurring

episodes of candidal vaginitis, but rather recurring episodes of vulvovaginal symptomatology due to a variety of other causes including non-infectious mechanisms. In order to exclude a diagnosis of RVVC, the patient should be seen and cultures performed on at least two occasions, preferably during periods of exacerbation of symptomatology. If two consecutively obtained vulvovaginal cultures are negative for *Candida* species, one can confidently exclude the diagnosis of RVVC. Common clinical conditions frequently mistakenly diagnosed as RVVC are shown in table I.

5. Treatment

Before initiating or selecting antifungal therapy, it is essential to confirm the diagnosis of RVVC by obtaining a vaginal culture and identifying the species responsible for the repeated episodes. Every effort should be made to eliminate underlying or predisposing factors when recognised (table II). In patients known to have diabetes, strict control of hyperglycaemia should be attempted. Without adequate control of diabetes, it may be impossible, in spite of use of a variety of anti-fungal agents, to eliminate the recurring and chronic nature of RVVC. In patients not known to have diabetes, it is unnecessary to perform a glucose tolerance test (GTT) in pre-menopausal, otherwise healthy adult females. However, in post-menopausal females who develop RVVC, a GTT should be obtained. Patients with a history of attacks of RVVC being precipitated by candy binges, alcohol ingestion or episodes of refined sugar excess should avoid these practices.

Table I. Differential diagnosis of recurrent vulvovaginal candidiasis

Other infectious causes
Recurrent bacterial vaginosis
Missed diagnosis: trichomoniasis sensitive to metronidazole
Resistant trichomoniasis
Unrecognised recurrent genital herpes
Non-infectious vulvovaginitis
Hypersensitivity, allergic and chemical vulvitis
Contact dermatitis
Atrophic vaginitis, vestibulitis
Idiopathic vestibulitis syndrome
Desquamative inflammatory vaginitis
Erosive lichen planus
Lichen sclerosus
Dermatoses (eczema, atopy, psoriasis)
Collagen vascular disease
Physiologic leukorrhoea

As a general rule, cessation of OCs rarely results reductions of the attack frequency of RVVC. Similarly, conversion of the patients to lower oestrogen containing OCs has not been shown to influence the outcome. Most practitioners would not stop OCs, *per se*, since control of infection can be obtained without this step. In post-menopausal females receiving HRT and with RVVC, if the HRT is considered important to the overall management of the patient, cessation of HRT is not essential since control of RVVC can be achieved by addition of suppressive antimycotic prophylaxis. In general, a high concentration of topical intravaginal oestrogen use is more hazardous. In women in whom RVVC is precipitated by repeated courses of antibacterials, it is unnecessary to place the patient on a long-term maintenance suppressive regimen and individual episodes can be prevented by use of prophylactic azole agents, either oral or topically, in conjunction with the needed antibacterial course. A personally suggested regimen is oral fluconazole 150mg administered at the start of antibacterials and once weekly throughout the duration of the antibacterial course. Secondary causes of RVVC and specific management are listed in table II.

Unfortunately, in the majority of patients with RVVC, an underlying cause and precipitating factor is not evident. Accordingly, the next step is to determine the species of the organism involved (figure 2). Since the majority of the patients will have azole susceptible *C. albicans*, the recommended treatment is an initial antifungal induction regimen aimed at not only controlling symptoms but achieving a culture negative status. In women with RVVC, failure to initiate a maintenance regimen will result in mycological and clinical relapse of vaginitis in 50% of patients within 3 months.[3] Once the vaginal cultures are negative following induction therapy, a long-term maintenance suppressive azole regimen, for 6 months, is immediately implemented without a

Table II. Causes and management of recurrent vulvovaginal candidiasis

Cause	Management
Primary (idiopathic)	Suppressive azole prophylaxis (6m)
Secondary	
Uncontrolled diabetes	Optimal control of diabetes
Non-diabetic refined sugar excess	Limit candy binges, carbohydrate excess in selected females
Oestrogen excess	Reduce exogenous oestrogen[a]
	oral contraception
	hormone replacement
	local oestrogen
IUD	Remove IUD[a]
Antibacterial-induced	Limit antibacterial use and when use essential use azole prophylaxis
Underlying vulvar dermatosis (lichen sclerosus)	Treat dermatosis and azole prophylaxis
Non-*albicans Candida* spp., *C. glabrata*, *C. krusei*	Topical boric acid, 4% flucytosine, nystatin chemoprophylaxis
Resistant *C. albicans* (rare)	Topical boric acid, 4% flucytosine or 3% amphotericin B, nystatin
HIV and other immunodeficiency	HAART and decrease immunosuppression

a Recommendation controversial and unsubstantiated.

HAART = highly active antiretroviral therapy; **IUD** = intrauterine device.

gap in therapy. This can be achieved with either a topical or the more convenient oral systemic route. The route of administration of the suppressive prophylactic anti-fungal and frequency of administration depends on the pharmacokinetics of the azole selected. Accordingly, oral regimens including daily ketoconazole 100mg have been highly effective.[9] Similar results appear to be obtained with fluconazole prescribed as a dose of 100–150mg once weekly.[10] This is because a single dose of fluconazole 150mg achieves therapeutic concentrations in the vaginal secretions and tissues for approximately 3–5 days.[11] Similarly, a single suppository of clotrimazole, in lactic acid, 500mg once weekly provides therapeutic concentrations for several days.[12] The efficacy of continuous maintenance therapy varies on the frequency with which the drugs are administered.[13,14] Accordingly, fluconazole or itraconazole administered once monthly results in a 50% reduction in the recurrence rate of candidal vaginitis. In contrast, when fluconazole is administered weekly, one can achieve greater than 90% reduction in attack rate and a similar success rate can be achieve with daily ketoconazole or itraconazole.[10]

The success of the maintenance suppressive azole regimens is a consequence of the fungistatic suppression of the vaginal population numbers to levels of below culture-detectable levels, and at low numbers, the concentrations of residual fungi are not associated with symptoms. Unfortunately, the organisms are frequently not eradicated from the lower genital tract. Accordingly, after cessation of maintenance suppressive therapy, which is usually recommended for approximately 6 months, 60–70% of patients will relapse, symptomatically, within 1–2 months of stopping the antifungal therapy. This recurrent episode of RVVC is culture positive and caused by the identical strain of *Candida* sp. responsible for the initial symptomatic pre-treatment episodes. The failure of the fungistatic azoles to eliminate organisms from the lower genital tract, co-exist with the persistence of the immunodeficiency or aberrant immunoresponse in the vagina to the offending pathogen. In approximately one-third of patients, cessation of maintenance therapy after 6 months is accompanied by complete remission. It is reasonable to stop the maintenance therapy after 6 months and observe the patients. With proven recurrences caused by identical organisms, one has no alternative but to reintroduce an induction regimen followed by the maintenance regimen, which should then be given for approximately 12 months.

A core group of women with idiopathic RVVC exist in whom continuous therapy over several years may be required in order to control these attacks.

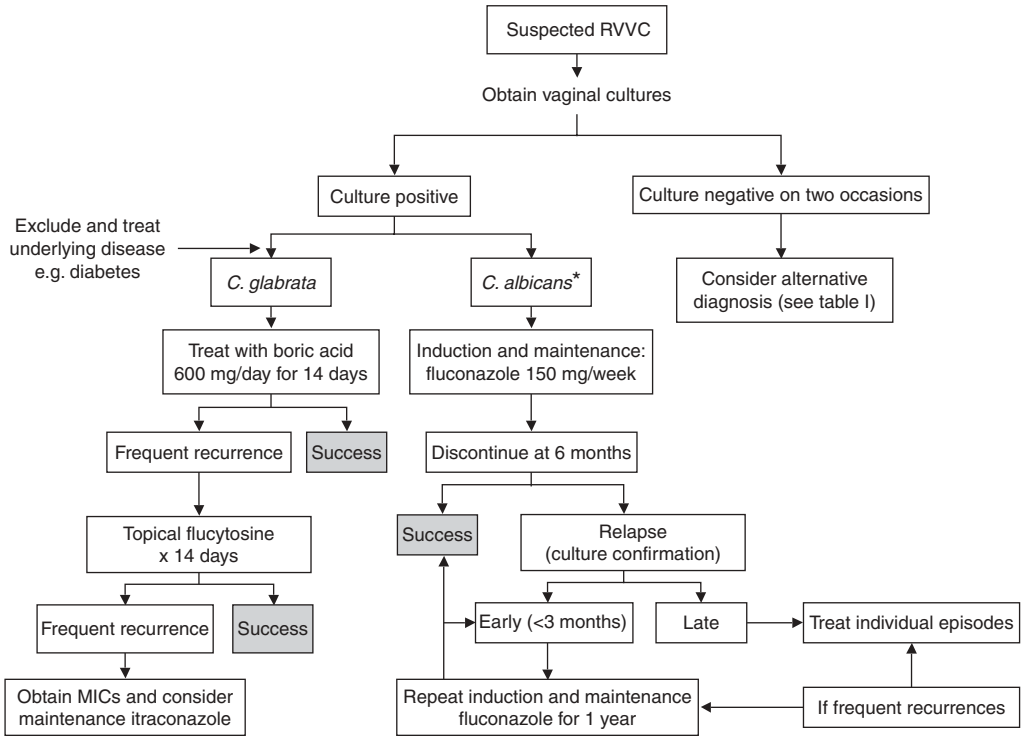

Fig. 2. Algorithm for treatment of recurrent vulvovaginal candidiasis (RVVC). **MIC** = minimum inhibitory concentration. * And other azole sensitive species.

Virtually all patients with idiopathic RVVC caused by *C. albicans* can be controlled, although not cured with maintenance regimens prescribed either orally or vaginally. It is apparent that oral therapy under these circumstances is far more acceptable and convenient than the topical therapy.[15] The issue of azole drug resistance is important. To date, acquisition of *C. albicans* resistance under these circumstances is extremely uncommon, although it is certainly reasonable in recurrent disease to confirm *C. albicans* susceptibility to a spectrum of azole agents. In general, antifungal drug resistance is usually suggested by lack of clinical response, as well as failed clearance of the organism, i.e. persistence rather than by recurrent disease.

The role of treatment of male sexual partners was reviewed by Sobel and no benefit was demonstrated in several large studies.[1] Similarly, a study by Fong using systemic ketoconazole therapy to treat male partners failed to reduce the recurrence rate in women with RVVC.[16] Nevertheless, Spinillo et al. in an uncontrolled study, did report decreased RVVC in women when attempts were made to eradicate all sources of *Candida* spp. in both partners.[17] Dennerstein reported a reduced rate of recurrence in RVVC in 15 patients during a 3-month period of depot medroxyprogesterone acetate therapy.[18] In a small study using patients as their own controls, Hilton et al. reported fewer episodes of VVC in women receiving oral yogurt.[19] Given the small numbers and lack of controls in this unblinded study, the role of yogurt in preventing candidal vaginitis remains unproven.[19] The majority of commercially available yogurt products do not contain viable lactobacilli. No evidence of human vaginal lactobacillus deficiency in patients with RVVC has been published.

An alternative approach to long-term maintenance antifungal therapy is the use of hyposensitisa-

tion with a *Candida* antigen preparation. Two small studies achieved encouraging results.[20,21]

5.1 Treatment of Recurrent Vulvovaginal Candidiasis (RVVC) Due to Non-*albicans Candida* Species

The most common non-*albicans Candida* species is *C. glabrata*.[4] It is not known whether the pathogenetic mechanisms responsible for RVVC due to *C. glabrata* are identical to those operative in RVVC due to azole-sensitive *C. albicans*. *In vitro* studies of comparative susceptibility of vaginal *C. albicans* and *C. glabrata* indicate that *C. glabrata* is approximately 10–100-fold less susceptibility to all azoles. Hence, susceptibility to recurrent diseases may be entirely independent of the host and due to microbial persistence consequent upon reduced drug susceptibility. The only drug more active against *C. glabrata* than *C. albicans* is flucytosine.[5] There is no reliable, proven, confirmed regimen for women who have recurrent RVVC due to *C. glabrata* (figure 2). An initial regimen of boric acid prescribed as 600 mg/day for 14 days per vagina, will result in eradication of the organism in approximately 70% of patients.[22] Whether or not these patients should be prescribed a maintenance regimen is unclear and the decision should be based on clinical response to this regimen. Accordingly, it is recommended that a single course of boric acid be prescribed. Should there be a recurrence, the first option would be to retreat with boric acid 600 mg/day for 14 days, followed by a maintenance regimen consisting either of alternate day boric acid for several weeks or switching to a maintenance regimen of intravaginal nystatin 100 000 U/day for 3–6 months. Studies confirming the efficacy of these maintenance regimens are not available. An alternative approach is to retreat the patient with flucytosine, prescribed intravaginally as a 17% solution for 14 days. Whether or not this should be followed by a maintenance regimen has not been determined.

5.2 RVVC in HIV Infected Women

Although several studies have suggested that RVVC is increased in HIV-infected women,[23] it should be emphasised that since RVVC is extremely common in immunocompetent, healthy, monogamous females, the mere confirmation of a diagnosis of RVVC does not justify testing any individual woman for HIV. A history of high-risk behavioural factors is more important in determining the need for HIV testing, than the finding of RVVC. In limited studies, the severity of RVVC does not appear to be different in HIV-infected women and in limited studies using fluconazole maintenance suppressive therapy, a similar positive effect in preventing recurring disease has already been demonstrated with fluconazole administered at a dose of 200mg once weekly.[24] HIV-positive women with RVVC can, therefore, be successfully treated with maintenance azole therapy in a manner similar to HIV-negative women.

6. Conclusion

The introduction of maintenance suppressive azole prophylaxis represents a major advance in controlling RVVC. Effective regimens that can be safely used are available which can be taken long-term (months and years) without concerns about the development of resistance. By the same token, curative therapy continues to evade us, in part due to a lack of understanding of immunopathogenesis of RVVC as well as absence of fungicidal agents capable of eradication and not just suppression of *Candida* species.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The author has no conflicts of interest that are directly relevant to the content of this manuscript.

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Correspondence and offprints: Dr *Jack D. Sobel*, Division of Infectious Diseases, Harper University Hospital, 3990 John R, Rm 4811, Detroit, MI 48201, USA.
E-mail: jsobel@intmed.wayne.edu