Chapter 1

Evidence-Based Management of Recurrent Vulvovaginal Candidiasis

Serene Thain\textsuperscript{1} and Thiam-Chye TAN\textsuperscript{1}

\textsuperscript{1}Department of Obstetrics and Gynaecology, KK Women’s and Children’s Hospital, Singapore

\textsuperscript{*}Corresponding Author: Thiam-Chye TAN, Department of Obstetrics and Gynaecology, KK Women’s and Children’s Hospital, Singapore, Email: drtctan@me.com

First Published March 26, 2016

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Abstract

Vulvo-vaginal candidiasis (VVC) is a common infection among women. 5-8% of women with acute infection experience recurrent vulvo-vaginal candidiasis (RVVC). There is currently no gold standard treatment for RVVC. Although antifungal agents such as imidazoles have been successfully used as first-line treatment for acute VVC, the effectiveness of these medications is limited for RVVC, and various reasons have been postulated to contribute to this. Here, we discuss the clinical features and pathogenesis of RVVC, and its usual recommended treatment regimens as well as newer upcoming potential alternative therapies for this chronic condition.

Epidemiology

Candida is a yeast that is commonly found in the vagina as part of normal flora, without causing symptoms. However, in certain situations, Candida can change from being a commensal organism to a pathogenic one, thereby causing symptoms of vulvovaginal candidiasis (VVC). Uncomplicated VVC affects 70-75% of women at least once during their lives, most frequently in young women of reproductive age. 40-50% of women will experience a recurrence [1]. Recurrent Vulvo-vaginal Candidiasis (RVVC) is usually defined as four or more episodes of symptomatic VVC within 1 year and affects up to 5-8% of adult women [2].
Microbiology

Most cases (85-95%) of uncomplicated VVC are caused by Candida albicans. The remainder are caused by non-albicans Candida spp, of which the most common is Candida glabrata. In RVVC, these less common Candida species may be implicated, and although clinically indistinguishable from infection caused by Candida albicans, they tend to be more resistant to treatment [2].

Clinical Features (Indistinguishable between symptoms caused by Candida albicans and non-albicans species)

Common symptoms include vaginal discharge, vulvar pruritus, dyspareuria and dysuria. On genital examination, the labia and vulva are often swollen, erythematous, with skin fissures commonly seen, and often accompanied by a thick, white vaginal discharge.

Pathogenesis of RVVC

The pathogenesis of RVVC is multifactorial. RVVC can be idiopathic or caused by several different mechanisms. These include:

1. Host factors: Uncontrolled diabetes mellitus, estrogen excess states (oral contraceptive pills, hormone replacement therapy, local estrogen administration, pregnancy), antibiotic-induced, immunosuppressive states (Systemic lupus erythematosus, human immunodeficiency virus, long-term corticosteroid use)

2. Genetic factors: Lewis blood group, African-American ethnicity, polymorphism

3. Behavioural factors: Orogenital sexual activity, contraceptive sponge/intrauterine contraceptive device use

4. Microbial factors: Non-albicans Candida spp)

Theories for Development of RVVC

Three theories have been put forth to explain why some women develop RVVC.

Intestinal Reservoir Theory

This theory suggests that persistence of Candida spp. organisms in the gastrointestinal tract later leads to reinfection of the vagina. This theory was originally based on uncontrolled data in the late 1970s which showed candida isolated from rectal cultures of women with RVVC being almost 100% identical to candida isolated from vaginal cultures, thereby suggesting the presence of a persistent intestinal reservoir of yeast [3]. The mechanism for RVVC was thus thought to be re-inoculation of the vagina from the persistent rectal focus. However, other studies in the literature have found a much lower concordance between rectal and vaginal cultures in patients with RVVC. In addition, 2 controlled trials showed that nystatin treatment given to reduce intestinal colonization with Candida albicans failed to prevent recurrent symptoms of vaginal in-
fection [4,5]. Results from these later studies make it less likely that the intestinal reservoir theory satisfactorily explains the cause of RVVC.

**Sexual Transmission Theory**

This theory suggests that the sexual partner is the reservoir or source for recurrent infection in the woman. A study that supports this theory found that asymptomatic colonisation of the male genitalia with candida was 4 times more common in the sexual partners of infected women than in those of non-infected women [6]. Also, strain typing methods have indicated that infected partners often harbour identical strains [7-9]. However, the role of sexual transmission in vaginal infection is still yet unknown, and treatment of the male partner does not appear to have an effect on the woman’s risk of recurrence [10,11].

**Vaginal Relapse Theory**

20-25% of women who test negative for candida immediately after treatment for vulvo-vaginal candidiasis subsequently test positive at 30 days post-treatment. The vaginal relapse theory thus postulates that the occurrence of RVVC is due to persistence of some strains of yeast despite anti-mycoytic treatment, suggesting a vaginal rather than intestinal reservoir of yeast. This is further supported by studies showing that the Candida strains isolated before and after treatment are identical in more than two-thirds of recurrences [12]. The recurrence is therefore thought to be not caused by a new infection, but rather caused by the persistence of organisms that increase in number and cause a new clinical episode when the environment permits. This is further promoted by certain exogenous factors discussed above as well as the possibility of lowered local vaginal immune response. The control of these factors is thus an important aspect in management of women with RVVC.

**Treatment Options**

There is currently no gold standard treatment for RVVC. Treatment should be individualised based on a comparison of effectiveness, convenience, potential side effects and cost. Treatment should also be via a multi-pronged approach, not limited to solely pharmacological therapies, but also aiming to eliminate factors that predispose an individual to vulvo-vaginal candidiasis. Before therapy, mycological culture should be obtained to confirm the diagnosis and to identify the specific Candida spp involved.

**General Advice and Lifestyle Changes**

General advice includes the avoidance of local irritants such as perfumed products and the maintenance of good perineal hygiene. Tight fitting synthetic clothing should also be avoided, although there is little evidence to
support this. The patient should be advised to use a soap substitute to clean the vulva area, and this should only be done externally and not more than once daily. Vaginal douching with feminine wash should be discouraged as this will affect the protective effect of normal vaginal commensals. In addition, an emollient can be used to moisturize the vulva skin.

**Medical Treatment**

Although no gold standard treatment regimen for RVVC currently exists, gynaecological experts have concurred that the recommended treatment should include the induction of clinical remission per acute episode, followed by a period of up to 6 months of maintenance therapy. This view is supported by a randomized controlled trial proving that maintenance therapy with weekly fluconazole for 6 months after clinical remission was superior with regards to the reduction of clinical recurrence [13]. However, regardless of which maintenance regime is chosen, symptomatic relapse is often seen in half of the women within a short time of cessation of treatment [13,14].

Table 1 shows some of the recommended drug regimens (induction and 6 months maintenance treatment) for RVVC.

**Table 1: Recommended drug regimens for RVVC.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing regimen</th>
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<tbody>
<tr>
<td><strong>Treatment for acute episode</strong></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>100mg vaginal pessary for 7 days</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>150mg orally single dose</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>200mg orally daily for 14 days</td>
</tr>
<tr>
<td>Terconazole cream</td>
<td>5g intravaginal for 3 days</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Two 100mg vaginal pessary twice weekly for 6 months</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>One 500mg pessary weekly for 6 months</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Two 200mg oral tablets for 5 days after menses for 6 months</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>100mg daily for 6 months (low risk of idiosyncratic drug-induced hepatitis. Monitor LFTs monthly)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>150mg orally once a month for 6 months</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>100mg weekly for 6 months</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200mg orally once a month for 6 months</td>
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**Alternative Treatment Approach (6-Week Regimen)**

An alternative approach to treatment of RVVC proposed is that of a six-week regimen with intravaginal butoconazole 2% slow release (SR) gel. The rationale for this proposed regimen is that of better patient compliance and increased susceptibility of the Candida species to this particular anti-mycotic drug. As discussed earlier, one possible contributing factor to RVVC is the higher prevalence of non-albicans species associated with RVVC that have a 10-30-fold reduced sensitivity to fluconazole, as well as lower susceptibility to other azoles (e.g.
ketoconazole, itraconazole) [15]. As such, eradication of these other types of non-albicans Candida species such as C. glabrata and C. krusei is often difficult. However, one study showed that eradication can be accomplished with adequate treatment using butoconazole, clotrimazole or miconazole. This particular study also showed that butoconazole was superior to miconazole and clotrimazole, with a low minimal inhibitory concentration of 90 at 24 and 48 hours against all species [16]. The difference between butoconazole and other imidazoles is that the latter play a major role in topical treatment and were developed initially for dermatologic use, and then subsequently applied to the treatment of vulvo-vaginal candidiasis. In contrast, butoconazole is a rare exception because it is specifically developed for the treatment of vulvovaginal candidiasis [17]. In addition, the SR formulation also helps to improve treatment compliance, as it is less messy and more convenient for patients, resulting in minimal interruption to their daily routine. Besides its SR properties, butoconazole also provides significantly faster relief of severe symptoms on the first post-treatment day [18,19]. It also avoids the main adverse effects of oral imidazoles such as gastrointestinal symptoms like abdominal pain and headache [20]. With oral medications, there is also a risk of drug interactions if the patient is taking other medications concurrently. Therefore, butoconazole has a much better safety profile compared to oral azoles [21]. Nonetheless, although the use of butoconazole in acute VVC compared to other forms of treatment has long been accepted as superior against all species of Candida, its use in RVVC still remains novel. A case report published by Heng et al. in 2012 looked at treatment of RVVC with sustained-release butoconazole pessary in two patients over a 6 week period, with achievement of good clinical and mycological cure within 6 months [22]. The recommended regimen was for an induction period of intravaginal butoconazole SR twice weekly for the first two weeks, followed by maintenance treatment of once a week for three to four weeks. Randomised trials are required to further compare and demonstrate the superiority of butoconazole to other azoles in order to determine its long-term efficacy.

**Alternative Therapies**

**Probiotics**

A 1992 crossover study assessed the association between the daily ingestion of yogurt containing Lactobacillus acidophilus and the prevention of RVVC [23]. In this study, women were assigned to a yogurt-free diet or a yogurt-containing diet. Only 13 of the 21 women completed the protocol, but it was found that women who ingested yogurt had a three-fold reduction in infection. The authors concluded that daily ingestion of an 8 oz of yogurt containing Lactobacillus acidophilus decreased the rate of candidal infection. More recently however, a review article looking at the role of probiotics for prevention of RVVC
found it to be controversial [24]. Some in-vitro studies and clinical trials showed positive results with respect to the effectiveness of some specific lactobacilli strains against Candida albicans. However, most of the trials either included a small sample of women or women with no confirmed episodes of VVC or were not placebo-controlled in nature. The review also noted that there were differences among the trials regarding the strain of the tested probiotic, its dosage and the duration of treatment, therefore making it difficult to draw reliable conclusions from the existing studies.

**IM Depo-Provera**

One study has suggested that the progestogen-only injectable may reduce a woman’s susceptibility to RVVC, possibly from its anovulatory effect and relative hypoestrogenism [25]. More studies need to be done to investigate the role of depo-provera as a preventive treatment for RVVC.

**Systemic Candida Antigen Hyposensitisation via the Cutaneous Route**

Meech et al. suggested that both Immunoglobulin E (IgE)-mediated and/or cellular-mediated hypersensitivity mechanisms may be involved in local candida infections [26]. In addition, Witkin et al. demonstrated in their study that the vaginal secretions of many women with RVVC contained anti-Candida IgE antibodies and detectable levels of prostaglandin E₂, leading to a speculation that a vaginal hypersensitivity response to Candida albicans may be associated with increased levels of prostaglandin E₂, which is capable of suppressing localised vaginal cell-mediated immune responses [27]. The loss of this localised vaginal defense mechanism can result in colonization by yeast leading to repetitive infections. In a small and limited uncontrolled study looking at hyposensitisation with laboratory-prepared Candida antigen, Rosedale and Browne achieved encouraging results [28]. This may be a promising alternative treatment for patients who are unable to tolerate maintenance azole suppressive treatment.

**Treatment of Male Partners**

There is currently no evidence to support treatment of asymptomatic male partners, and therefore routine treatment should therefore be deemed unnecessary [29].

**Vaccine**

Currently, a multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trial is underway to evaluate the safety, tolerability, immunogenicity and efficacy of a NDV-3 vaccine developed for the prevention of episodes of VVC in patients with RVVC. This vaccine contains a recombinant form of the Candida albicans surface protein Als3, which facilitates adherence to and invasion of human endothelial cells. This trial follows a preclinical study in a model of VVC, which demonstrated that NDV-3 induced potent and protective immune responses, as well as 2 successful Phase 1 studies, which demonstrated
that NDV-3 was safe, well-tolerated and induced strong antibody and T-cell immune responses in healthy adults. 188 patients have been enrolled into the Phase 1b/2a trial, of which the results are currently pending. The estimated study completion date is in May 2016.

**Conclusion**

In conclusion, RVVC is a highly troublesome condition for women who experience it. There is currently no optimal treatment for RVVC, but the approach to the treatment of this condition should be multi-pronged in view of its multifactorial pathogenesis. Research is currently underway to develop new approaches besides that of anti-mycotic treatment for the management of RVVC.

**References**

12. Chong PP, Lee YL, Tan BC, Ng KP. Genetic relat-


23. Hilton E, Isenberg HD, Alperstein P, France K, Bo-
Candidiasis


