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## SPECIAL ARTICLE

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# Acute Vaginal Candidiasis: A review of treatment guidelines and Siriraj experience

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### ABSTRACT

Acute vaginal candidiasis (VC) is a leading cause of abnormal vaginal discharge at gynecologic clinics. The most common causative organism is *Candida albicans*, which is one of the vaginal normal flora. Therefore, VC is not considered as being a sexually-transmitted disease (STD). Host factors such as a disturbance of vaginal ecosystem, a prolonged use of antibiotics and individual hormonal effect appear to precipitate the condition. Although symptoms and signs of VC are unique, the diagnosis also requires a basic tool like a microscope. Azole antifungals are recommended as the first-line treatment in all guidelines. However, lifestyle modification is apparently as important. As the Siriraj Female STD Clinic (Clinic 309) has been taking of this group of patients and has conducted some clinical trials on this issue, we would like to review current treatment guidelines of acute VC and to share some of our experience.

**Keywords:** vaginal candidiasis, treatment guideline, Siriraj experience.

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## Introduction

Vaginal candidiasis (VC) is a leading cause of abnormal vaginal discharge for women<sup>(1, 2)</sup>. The most common pathogen, causing 80-90% of cases, is *Candida albicans*<sup>(2)</sup>. Other pathogens include *C. glabrata*, *C. tropicalis*, and *C. krusei*. *C. albicans* is a normal vaginal flora which causes symptoms only when there is a substantial increase of pathogens, so this disease is not

considered as a sexually-transmitted disease (STD). According to 183 case-based data from the Siriraj Female STD Clinic, the pathogens causing acute VC were as follows: *C. albicans* 94.6%, non-*albicans Candida* 2.7% (*C. glabrata* 3 cases, *C. tropicalis* 1 case, *C. nivariensis* 1 case); and both *C. albicans* and non-*albicans Candida* 2.7% (*C. glabrata* 2 cases, *C. tropicalis* 2 cases, *C. nivariensis* 1 case).

According to the Center for Disease Control and prevention (CDC), VC is classified into complicated and uncomplicated vaginal candidiasis based on the severity of the disease<sup>(3)</sup>. Recently, the British Association for Sexual Health and HIV (BASHH) suggests disease duration-based classification into acute VC and recurrent VC. The recurrent VC is defined as having at least 4 recurrences within a previous year, with at least 2 recurrences confirmed by either microscopic diagnosis or culture whilst having any symptoms<sup>(4)</sup>.

## Risk factors

The risk factors of vaginal candidiasis are associated with internal factors of individual patient rather than the severity of pathogens, which are commonly related to blood sugar level, long-term use of antibiotics, additional hormonal treatment (estrogen-containing contraceptive pills, hormonal replacement in menopausal period), stress or mood change, iron deficiency anemia, and excessive cleansing of external genitalia<sup>(4)</sup>.

According to the study of non-pregnant Chinese women including 97 cases of VC and 87 controls<sup>(5)</sup>, the

following risk factors were found: previous vaginitis (odds ratio (OR) 9.00, 95% confidence interval (CI) 2.82-28.76); frequent wearing of tight clothing (OR 6.61, 95% CI 1.37-27.75); frequent dessert or sweet drink consumption (OR 6.33, 95% CI 2.17-18.52); no condom use (OR 3.77, 95% CI 1.90-4.12); previous uterine curettage (OR 3.47, 95% CI 1.32-9.15); and having  $\geq 2$  partners (OR 3.22, 95% CI 1.04-9.96).

## Diagnosis and differential diagnosis<sup>(4)</sup>

The signs and symptoms of VC are unique, including itchiness, curd-like vaginal discharge, and lesions on external genitalia such as erythematous skin, swelling and abrasion. However, the diagnosis of VC should not be based on only symptoms, but should also be confirmed by laboratory investigation. Table 1 shows diagnostic accuracy of using symptoms, signs and microscopic examination for diagnosing VC. Despite the highest sensitivity of symptoms, other differential diagnosis should be concerned, including dermatitis, eczema, lichen sclerosus, vulvodynia, aerobic vaginitis, and cytolytic vaginosis.

**Table 1.** Diagnostic accuracy for detecting any *Candida* spp. when using positive culture result as the gold standard (n=183).

	Positive culture result (n=42)				No growth (n=141)	Diagnostic accuracy for detecting any <i>Candida</i> spp.			
	Total (n=42)	<i>C. albicans</i> (n=30)	Non- <i>albicans</i> (n=9)	Mixed (n=3)		SN	SP	PPV	NPV
Symptoms	20 (47.6)	14 (46.7)	4 (44.4)	2 (66.7)	20 (14.2)	47.6%	85.8%	50.0%	84.6%
Curd-like discharge	10 (23.8)	7 (23.3)	2 (22.2)	1 (33.3)	5 (3.5)	23.8%	96.5%	66.7%	81.0%
Detection of pseudohyphae	9 (21.4)	7 (23.3)	2 (22.2)	0	8 (5.7)	21.4%	94.3%	52.9%	80.1%

SN: sensitivity, SP: specificity, PPV: positive predictive value, NPV: negative predictive value

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Examination of vaginal discharge under a microscope is the basic method with acceptable reliability. The culture of vaginal discharge is suitable only for recurrent VC since drug susceptibility test can be done resulting in quicker treatment response. Polymerase chain reaction (PCR) does not play any diagnostic role in routine practice.

*Candida* spp. detected on Pap smear can be

either colonization or infection. There was no association between detection of *Candida* spp. in Pap smear and clinical symptoms as well as objective abnormal vaginal discharge<sup>(6)</sup>. As a result, Pap smear should not be a routine diagnostic tool of VC<sup>(7)</sup>. However, the data from the Siriraj Female STD Clinic showed that, of 64 women, who presented with acute VC and had detected fungus in their latest Pap smear,

22 (34.4%) had neither symptoms nor curd-like discharge on the Pap smear day. Re-evaluation is thus suggested for those who did not receive VC treatment since the Pap smear was taken.

Screening for other STDs is currently not recommended. Other additional laboratory investigations, such as screening for diabetes mellitus and iron deficiency anemia, are individually considered.

**Table 2.** Treatment guidelines for treating women with acute vaginal candidiasis.

	<b>Treatment regimen</b>
CDC2015 <sup>(9)</sup>	<ul style="list-style-type: none"> <li>- Clotrimazole 1% cream 5 g intra-vagina daily for 7-14 days</li> <li>- Clotrimazole 2% cream 5 g intra-vagina daily for 3 days</li> <li>- Miconazole 2% cream 5 g intra-vagina daily for 7 days</li> <li>- Miconazole 4% cream 5 g intra-vagina daily for 3 days</li> <li>- Miconazole 100 mg intra-vagina daily for 7 days</li> <li>- Miconazole 200 mg intra-vagina daily for 3 days</li> <li>- Miconazole 1,200 mg a single vaginal dose</li> <li>- Tioconazole 6.5% ointment 5 g intra-vagina in a single application</li> <li>- Butoconazole 2% cream 5 g intra-vagina in a single application</li> <li>- Terconazole 0.4% cream 5 g intra-vagina daily for 7 days</li> <li>- Terconazole 0.8% cream 5 g intra-vagina daily for 3 days</li> <li>- Terconazole 80 mg intra-vagina daily for 3 days</li> <li>- Fluconazole 150 mg a single oral dose</li> </ul>
ASHA2018 <sup>(12)</sup>	<p><b>Recommended regimen</b></p> <p>Vaginal azole creams (e.g. clotrimazole 10% vaginal cream, 1 applicator intra-vagina daily for 3-7 days)</p> <p><b>Alternative regimen</b></p> <p>Fluconazole 150 mg a single oral dose</p>
IUSTI2018 <sup>(13)</sup>	<ul style="list-style-type: none"> <li>- Fluconazole 150 mg a single oral dose</li> <li>- Itraconazole 200mg orally twice daily for 1 day</li> <li>- Clotrimazole, a single 500mg vaginal dose</li> <li>- Clotrimazole 200mg intra-vagina daily for 3 days</li> <li>- Miconazole 1200mg a single vaginal dose</li> <li>- Miconazole 400mg intra-vagina daily for 3 days</li> <li>- Econazole vaginal pessary 150mg as a single dose</li> </ul>
BASHH2019 <sup>(4)</sup>	<p><b>Recommended regimen</b></p> <ul style="list-style-type: none"> <li>- Fluconazole 150 mg a single oral dose</li> <li>- Clotrimazole, a single 500mg vaginal dose</li> </ul> <p><b>Alternative regimen</b></p> <ul style="list-style-type: none"> <li>- Clotrimazole cream(10%) 5gm, a single vaginal dose</li> <li>- Clotrimazole 200mg intra-vagina for 3 nights</li> <li>- Econazole 150mg, a single vaginal dose</li> <li>- Fenticonazole 600mg, a single vaginal dose or 200mg intra-vagina for 3 nights</li> <li>- Itraconazole 200mg per oral twice daily for 1 day</li> <li>- Miconazole 1200mg, a single vaginal dose, or 400mg intra-vagina for 3 nights</li> <li>- Miconazole cream(2%) 5g intra-vagina for 7 nights</li> </ul>

ASHA: Australian Sexual health Alliance, BASHH: British Association for Sexual Health and HIV, CDC: Center for Disease Control and Prevention, IUSTI: International Union against Sexually Transmitted Infections

## Management

Table 2 depicts current VC treatment guidelines provided by different organizations<sup>(3-4, 12-13)</sup>. All of them agree on using azole group as the first-line treatment because *C. albicans*, the main etiologic organism, responds well to the medication. Its mechanism of action is to inhibit an important enzyme in ergosterol biosynthesis, causing a weakened or absent cell wall. As host factor seems to be more important, advice for lifestyle modification and proper self-care must be underlined. At the Siriraj Female STD Clinic, all women with VC are sent to see a nurse before leaving. They are advised and educated about all information shown in Table 3.

Azole-group medications can be administered orally, intra-vaginally and topically. Based on 10-year data, any of the aforementioned forms has an efficacy of more than 80% in curing acute VC<sup>(8)</sup>. Nonetheless, the oral form is prohibited among pregnant and lactating women; and the vaginal form impairs contraceptive effectiveness of condoms and may cause vaginal irritation. Moreover, there should be

caution of drug-drug interaction, especially those causing prolonged QT interval such as some anti-psychotic drugs (haloperidol, thioridazine), some anti-depressive drugs (amitriptyline, imipramine, fluoxetine, sertraline), some antibiotics (levofloxacin, erythromycin), anti-arrhythmic drugs (amiodarone, procainamide) etc<sup>(9-11)</sup>.

For over 30 years, the Siriraj Female STD Clinic has not only been taking care of women with VC but also conducted clinical trials in Thai women as shown in Table 4. We have some experience using new VC treatment medications like sertaconazole 300mg vaginal ovule (Zalain<sup>®</sup>) and a vaginal drug combining metronidazole 750mg and miconazole 200mg (Neopenotrans forte<sup>®</sup>). We found that Zalain<sup>®</sup> has a comparable efficacy with 500mg clotrimazole vaginal tablet for treating both pregnant and non-pregnant women with acute VC. Moreover, there was no adverse pregnancy outcome. Neopenotrans forte<sup>®</sup> causes mild vaginal irritation on the first few days of usage and results in good clinical response. So far, no adverse pregnancy outcomes have been reported.

**Table 3.** Advice for patients with vaginal candidiasis at the Siriraj Female STD Clinic.

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When patients are diagnosed with vaginal candidiasis, they will proceed to see a nurse for the following advice regarding disease and self-care.

1. All patients will be assessed by questionnaire about their knowledge regarding vaginal candidiasis and vaginal health care, and then the nurse provides additional information and corrects misunderstandings. Open discussion is always welcomed. Patients will be given a leaflet about vaginal candidiasis for further learning.
2. Patients prescribed vaginal suppository medication will watch a teaching video about how to insert the medication and will be provided a hand-on practice with a manikin which is an innovative product of the unit.

Advice regarding self-care for women with vaginal candidiasis

- Avoid wearing tight garments. Cotton material is preferable.
- Avoid excessive genital cleansing, as well as vaginal douching
- Change quickly out of wet clothing
- Minimize eating carbohydrate- and sugar-rich food
- Always stay healthy

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**Table 4.** Clinical trials of vaginal candidiasis being conducted at the Siriraj Female STD Clinic.

Year	Studies	Outcome measures	Results
1985 <sup>(14)</sup>	Single arm: - Micronazole 400 mg gelatin capsule OD, 3days (n=86), pregnant women 32/86 (37.2%)	- symptoms and signs - Microscopy - Fungal culture	- Complete resolution of symptoms and signs at 1 week: pruritus 66.3%, vaginal discharge 38.4%, burning sensation 86.1%, dysuria 91.9%, dyspareunia 97.6% - Absence of pseudohyphae under microscopy detected at 1 week 93.1%, at 4 weeks 93.1% - Negative culture for <i>C. albicans</i> at 1 week 87.3%, at 4 weeks 79.1% - No difference of cure rate between pregnant and non-pregnant women
1986 <sup>(15)</sup>	Single arm: - Ketoconazole 400 mg oral OD, 5 days (n=31)	- symptoms and signs - Microscopy - Fungal culture	- Clinical cure rate (absence of all symptoms) at 1 week 100%, at 4 weeks 96.0% - Microscopic cure rate at 1 week 83.8%, at 4 weeks 72% - Culture cure rate at 1 weeks 83.9%, at 4 weeks 72%
1987 <sup>(16)</sup>	Single arm: - Econazole 150mg intra-vagina hs, 3 nights (n=43)	- symptoms and signs - Fungal culture	- Clinical cure rate at 1 week 97.7%, at 4 weeks 88.4% - Culture cure rate at 1 weeks 83.7%, at 4 weeks 67.4%
1992 <sup>(17)</sup>	Single arm: - Itraconazole 200 mg oral bid, one day (n=59)	- symptoms and signs - Fungal culture	- Clinical cure rate at 1 week 89% , at 4 weeks 90% - Culture cure rate at 1 weeks 83.3%, at 4 weeks 69.6%
2010 <sup>(18)</sup>	3 arms - Sertaconazole 500 mg intra-vagina, single dose (n=62) - Fluconazole 150 mg (n=63) - Clotrimazole 100 mg vaginal tablets, 6 nights (n=52)	- Fungal culture	- Culture cure rate at 1 week: sertaconazole 53.0%, fluconazole 61.7%. clotrimazole 58.1% - Positive culture at 4 weeks: sertaconazole 10.6%, fluconazole 33.3%, clotrimazole 20%
2020 <sup>(19)</sup>	2 arms (RCT) - Clotrimazole (CT) 100 mg intra-vagina hs, 6 nights (n=76) - Dequalinium chloride (DQC) 10 mg intra-vagina hs, 6 nights (n=74)	- symptoms and signs - Microscopy - Fungal culture	- Clinical cure rate at 1 week CT 94.7% vs DQC 75%, at 4 weeks CT 85.1% vs DQC 84.9% - Microscopic cure rate at 1 week CT 85.3% vs DQC 74.7%, at 4 weeks CT 75.7% vs DQC 57.6% - Culture cure rate at 1 week CT 66.2% vs DQC 34.3%, at 4 weeks CT 63.4% vs DQC 30.3%

## Management in specific groups

### Women with severe symptoms

Severe symptoms are defined as also having

markedly inflamed external genitalia. CDC recommends oral treatment with fluconazole 150 mg taken twice 72 hours apart or a longer course of topical treatment for

7-14 days<sup>(3)</sup>. BASHH recommends the same dosage of fluconazole or clotrimazole 500 mg, or miconazole 1,200 mg given as a vaginal suppository once daily and again 72 hours later<sup>(4)</sup>. Low-potency corticosteroid cream and anti-histamine lead to quicker relief.

### **Women with non-albicans Candida and azole resistance**

BASHH recommends nystatin 100,000 units intra-vagina at night for 12-14 consecutive nights as the first-line drug<sup>(4)</sup>. In Thailand, the only nystatin vaginal tablet is in the form of combination drug with benzalkonium chloride and diiodohydroxyquinoline (Gynecon<sup>®</sup>). The alternative regimen is not widely available in Thailand, including one of the followings: boric acid 600 mg intra-vagina daily for 14 days, amphotericin B 50 mg intra-vagina daily for 14 days or flucytosine 5 g cream or 1g pessary intra-vagina with amphotericin or nystatin daily for 14 days.

### **Pregnant and lactating women**

The oral form of antifungal medications should be avoided; however, taking this medication during pregnancy is not an indication for termination of pregnancy. Based on current data, there is no association between VC and preterm delivery or low-birth-weight newborn<sup>(20)</sup>. VC is more prevalent and more recurrent among pregnant women. The longer course and the higher dose of medication are suggested. BASHH recommends clotrimazole 500mg intra-vagina for up to 7 nights and the alternative regimen is one of the followings: clotrimazole vaginal cream (10%) 5 g daily for 7 nights, clotrimazole 200 mg intra-vagina daily for 7 nights, econazole 150 mg intra-vagina for 7 nights, miconazole 400 mg intra-vagina for 7 nights or miconazole cream (2%) 5 g intra-vagina for 7 nights<sup>(4)</sup>.

### **Women taking combined hormonal contraception or hormonal therapy replacement in menopausal period<sup>(4)</sup>**

Treatment is also similar to other groups, but data regarding association between combined hormonal contraception or hormonal therapy replacement in menopausal period and VC should be informed,

however decision to halt treatment should be individualized. Progestin only contraceptives theoretically should reduce risk because estrogen level decreases; however, there is no explicit data in pragmatic decision.

### **Women with diabetes mellitus or human immunodeficiency virus infection<sup>(4)</sup>**

These women are treated as those in other groups. However, longer course of treatment may be needed and long-term follow-ups are needed. Based on our experience, following the well-controlled glycemic and immune status, there are less recurrent episodes.

### **Follow-up after treatment and partner management<sup>(4)</sup>**

A follow-up after treatment of acute VC is not needed unless there are recurrent episodes. Regarding partner management, treatment is indicated only when the partner has symptoms.

## **Conclusion**

Vaginal candidiasis has been a challenging problem for obstetricians and gynecologists since it can occur frequently and there are myriad involving factors. Even though azole group medications result in high treatment efficacy, another important management is lifestyle modification in relation to food, mind, and hygienic care of genitalia. Good collaboration between medical personnel and patients themselves helps alleviate disease recurrence.

## **Potential conflicts of interest**

The authors declare no conflict of interest.

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