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## SPECIAL ARTICLE

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# Acute Vaginal Candidiasis: Another Step Forward to the Deeper Understanding

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## ABSTRACT

Vaginal candidiasis (VC) arises from an imbalance in the vaginal milieu influenced by intrinsic and extrinsic factors, including diet, hormonal fluctuations, and genital hygiene. The predominant causative organisms are *Candida* spp., with *C. albicans* being the most prevalent. *Candida* spp. are part of the normal flora residing on the vaginal mucosa and other mucous membranes throughout the body. The human body employs numerous mechanisms to maintain equilibrium between these fungi and commensal bacteria. Any disruption of this equilibrium can result in *Candida* overgrowth, manifesting as symptoms such as profuse vaginal discharge or burning and itching of the vulvar and vaginal region. In 2022, the Royal Thai College of Obstetricians and Gynaecologists issued treatment guidelines for reproductive-age women presenting with abnormal vaginal discharge. These guidelines recommend various pharmacological regimens and behavior modifications to minimize future recurrence. Nevertheless, experts in real-world practice often suggest adaptations to these regimens to enhance therapeutic outcomes. The Siriraj Female Sexually Transmitted Infections Clinic regularly manages VC cases and implements a 2-week follow-up protocol for all patients. Given that VC is the most common diagnosis for abnormal vaginal discharge at the clinic, significant expertise has been accumulated in treating the condition. The collected perceived insights can be invaluable for fellow professionals, potentially broadening service perspectives and catalyzing further research.

**Keywords:** vaginal candidiasis, reproductive-aged, treatment, alternative, pap smear.

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## Introduction

Vaginal imbalances are commonplace and can lead to abnormal proliferation of vaginal organisms. These imbalances can result in conditions such as an overgrowth of fungi (fungal vaginitis) and a surge in anaerobic bacteria (bacterial vaginosis; BV), aerobic bacteria (aerobic vaginitis; AV), or *Lactobacilli* (cytolytic vaginitis; CV)<sup>(1)</sup>. The most prevalent conditions are bacterial vaginosis and fungal vaginitis<sup>(2)</sup>. The most common type of fungal vaginitis is caused by the genus *Candida*, and it is often referred to as vaginal candidiasis (VC). This condition is caused by an increase in *Candida* spp., predominantly *C. albicans*, a component of the vaginal flora<sup>(3)</sup>. The symptoms of VC include a profuse, curd-like discharge that might separate into a watery, yogurt-like consistency, vulvar and vaginal itching, redness, swelling, abrasiveness, dysuria, and dyspareunia<sup>(1)</sup>. Despite the previous report showing that untreated VC in pregnant women was associated with an increased risk of preterm labor<sup>(4)</sup>, recent evidence reveals some controversy for this issue<sup>(5)</sup>.

Affecting women of all ethnicities, VC is estimated to occur in 75% of women at some point in their lives<sup>(6)</sup>. Studies indicate that 10%–20% of asymptomatic, nonpregnant women harbor VC<sup>(3)</sup>, with the prevalence rising to 20% in second-trimester pregnant women and up to 52% in the third trimester<sup>(7, 8)</sup>. Understanding the mechanisms driving the transition from a normal balance of organisms to a disease state, alongside the available treatment modalities and their limitations, is crucial. VC is typically categorized into acute and recurrent types<sup>(9)</sup>. Recurrent VC is defined as having at least 4 episodes, including the present one, in prior one year; and requires a much longer course of treatment.

In 2022, the Royal Thai College of Obstetricians and Gynaecologists issued guidelines for the management of reproductive-age women with abnormal vaginal discharge. These guidelines recommend various drug regimens and behavioral modifications to minimize the recurrence risk. However, some experts, including our staff members, argue for

adjusting specific regimens to optimize therapeutic outcomes<sup>(10)</sup>. Consequently, the Siriraj Female Sexually Transmitted Diseases Clinic has expanded its medication offerings for treatment. In the past three years, all patients were advised to return for re-evaluation. Those without cure received secondary treatment and few needed the third or fourth regimen. This article focuses primarily on acute vaginal candidiasis, the most prevalent type, and addresses the challenge of managing patients with fungi detected in Pap smears—a frequent issue in medical practice.

## *Candida* spp. and Immunopathology

*Candida* spp. are fungi from the family Saccharomycetaceae, a family of yeasts that reproduce by budding and prefer carbohydrate-rich environments, on which they feed. The *Candida* genus comprises more than 30 pathogenic species, with *C. albicans* being the most prevalent. Notably, *C. albicans* can morph between the yeast and pseudohyphae forms. Cellularly, *C. albicans* is characterized outside by a cell wall, followed by a plasma membrane, cytoplasm, and various organelles. The wall has a core skeleton composed of  $\beta$ -glucan and chitin, providing structural strength and ensuring shape retention. The outermost layer of the wall is coated with mannan, which exhibits low permeability. The innermost layer of the cell wall, just before the plasma membrane, is made of chitin, which is particularly robust<sup>(11)</sup>. The plasma membrane itself is a bilipid layer comprising ergosterol and phospholipids. The external structures of *Candida* spp. serve as targets for antifungal drugs<sup>(12)</sup>.

*C. albicans* is a component of the normal flora that inhabits the mucous membranes of the intestines, oral cavity, and vagina. However, when these mucosal barriers weaken and local immunity is compromised, *Candida* spp. multiply and induce disease. The pathogenesis of this fungus arises from a combination of several virulence factors. Polymorphism allows the fungi to assume various shapes. Their invasive capabilities permit cell entry via induced endocytosis and active penetration. This intrusion leads to an accumulation of the toxin called candidalysin on the

surface resulting in inflammatory mucosal damage that later destroys host's innate immune cells. Furthermore, the capacity of *Candida* spp. for adhesion and biofilm formation enables them to bind to both biotic (living) and abiotic (nonliving) surfaces, such as catheters and intrauterine devices (IUDs). These biofilms not only provide a protective habitat for the fungi, but also protect them from external threats. Genetic and metabolic plasticity endows *Candida* spp. with significant metabolic flexibility, facilitating environmental adaptation and rapid evolutionary modification. This plasticity allows the fungi to survive pressure and stress, especially from antifungal drugs and host defense responses. Furthermore, the robust structure of the cell wall equips it with resilience against external factors and offers mechanisms to evade host immune detection<sup>(13)</sup>.

A healthy vagina sustains a balanced mix of bacteria and fungi, and *Lactobacilli* playing a pivotal role in the preservation of this equilibrium. *Lactobacilli* generate lactic acid and hydrogen peroxide that neutralize other organisms and form a biofilm on the vaginal walls<sup>(14)</sup>. A reduction in *Lactobacillus* levels allows the proliferation of resident fungi, leading to disease. The progression of fungal vaginitis entails 3 stages: adhesion, blastopore germination, and invasion. Notably, *C. albicans* exhibits a superior adhesive capability<sup>(15)</sup>. The presence of estrogen potentiates this adhesion by increasing the surface exposure of glycoprotein complexes, which act as receptors<sup>(16)</sup>. Moreover, *Lactobacilli* secrete bacteriocin, thereby impeding fungal germination, and compete with *C. albicans* for limited nutrients<sup>(17)</sup>.

When fungal hyphae extend, they attempt to infiltrate the vaginal wall. In response, the body deploys neutrophils, macrophages, and dendritic cells, leading to the release of proinflammatory cytokines and chemokines that further recruit macrophages and neutrophils. Simultaneously, fungi secrete candidalysin, inflicting direct damage on the epithelium. The epithelium retaliates by releasing antimicrobial peptides that restrict fungal growth, damage-associated molecular patterns that amplify

inflammation, and additional chemokines and cytokines. Although neutrophils can eliminate *Candida* through phagocytosis, the fungi's ability to morph from yeast to hyphae complicates this process. After phagocytosis, the fungus continues its yeast-to-hyphae transformation, resulting in neutrophil death. Another contributing factor involves the formation of neutrophil extracellular traps, leading to further neutrophil death. Following these events, adaptive immunity is activated, prompting T cells to target fungi and promoting dendritic cell maturation to enhance fungal elimination. However, fungi are also capable of adaptation, thus increasing their resilience to external conditions. This dual mechanism of inflammation and cellular destruction provides fungi with additional nutrients from host cells, which supports their proliferation<sup>(13)</sup>.

The regulation of *Candida* populations is location dependent. For instance, oral mucosal *Candida* levels are modulated by T cells (Th17 immunity), whereas the vaginal environment is controlled by neutrophil-mediated immunopathology. This difference becomes apparent in patients living with human immunodeficiency virus (HIV): a direct impact on T cells leads to increased oropharyngeal candidiasis, but the incidence of VC remains stable<sup>(13)</sup>.

## Factors Impacting Vaginal Balance

Vaginal imbalance, induced by both intrinsic and extrinsic factors, can persistently occur and eventually culminate in VC. Intrinsic factors are sex hormone levels and menstrual blood. Specifically, estrogen plays a pivotal role in *Candida* pathogenesis<sup>(16)</sup>, while menstruation disrupts vaginal balance by diminishing *Lactobacillus* populations. Contraceptive methods that induce spotting or elevate estrogen levels can likewise foster *Candida* proliferation. Moreover, vaginal douching can disrupt *Lactobacillus* activity and amplify VC risks<sup>(18)</sup>, with a higher incidence of nonalbicans *Candida* noted<sup>(19)</sup>. A diet abundant in sugary foods promotes fungal growth<sup>(20)</sup>. Our experience has shown that the decreased intake of a sugar-rich diet results in an increase in the culture-based cure rate<sup>(3)</sup>. Pregnancy,

characterized by fluctuating blood sugar levels and escalated estrogen, fosters VC development—a scenario also seen in individuals with diabetes. Long-term antibiotic use can dramatically reduce *Lactobacillus* numbers, precipitating VC. Although tight clothing has not been directly associated with VC<sup>(21)</sup>, it should be avoided during symptomatic periods. Additional extrinsic factors include stress<sup>(22)</sup>, iron deficiency anemia, and excessive genital cleaning<sup>(9)</sup>.

## Diagnosis

The diagnosis of VC necessitates laboratory confirmation, such as microscopic examination of the vaginal discharge diluted with a saline solution. When this is combined with a 10% potassium hydroxide solution, pseudohyphae become visible, as the solution is unable to degrade chitin, a crucial

cell wall component. Nevertheless, relying solely on visual examination of vaginal discharge yields limited diagnostic sensitivity<sup>(23)</sup>. Culture is beneficial for recurrent VC or cases where symptoms are present without detectable pseudohyphae under microscopy. Conversely, molecular testing offers limited value<sup>(9)</sup>.

The differential diagnoses of excessive discharge combining with vaginal itching are trichomoniasis, cytolytic vaginitis, and aerobic vaginitis<sup>(1)</sup>. They can be differentiated by wet preparation (proportion of leukocytes and epithelial cells) and vaginal pH<sup>(24)</sup>. The Siriraj Female Sexually Transmitted Infections Clinic has provided a 5-minute long educational tool on wet preparation for medical students and healthcare providers (Fig. 1). Our experience has shown that briefly reviewing the online tool has a great impact on the recall to perform effective wet preparation<sup>(25)</sup>.



**Fig. 1.** QR code of an on-line educational tool on wet preparation

Source: Unit of Infectious Diseases, Department of Obstetrics and Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University

When primary symptoms are itching in the external genitalia, the differential diagnoses expand to four possible groups; chronic inflammatory dermatoses, preinvasive lesions, infections and secondary causes<sup>(26)</sup>. Chronic inflammatory dermatoses include lichen sclerosus, lichen planus, contact dermatitis, eczema, and psoriasis. Preinvasive lesions include Paget's disease, melanoma in situ, and vulvar intraepithelial neoplasia. Infections include herpes genitalis, genital wart and fungal infection. Secondary causes include allergy, diabetes mellitus, shaving, tight clothing and psychological

cause (vulvodynia). Interestingly, our previous report showed that 10% of women presenting with anogenital warts concurrently had VC<sup>(27)</sup>.

Coinfections with other conditions are common, particularly with bacterial vaginosis<sup>(28)</sup>, due to a similar reduction in *Lactobacilli*. In response to environmental stressors, anaerobes and *Candida* collaboratively form a mixed biofilm that provides protection. *Candida*'s low-oxygen biofilm enables rapid growth of anaerobes, even in the presence of potentially higher oxygen levels outside the biofilm<sup>(28)</sup>. These biofilms play an important role in therapeutic

response and recurrence, with biofilms dominated by multiple *Candida* strains further complicating treatment strategies<sup>(29)</sup>.

Treatment

In line with the treatment guidelines provided by the Center for Disease Control and Prevention and the British Association for Sexual Health and

HIV<sup>(9, 30)</sup>, the Royal Thai College of Obstetricians and Gynaecologists has established guidelines for the treatment of reproductive-age women with abnormal vaginal discharge. The guidelines were informed by practices from multiple countries, and they factored in drugs used in Thailand. They include recommendations for acute VC treatment (Table 1)<sup>(24)</sup>.

**Table 1.** The Royal Thai College of Obstetricians and Gynaecologists’ Treatment Guidelines for Reproductive-Age Women with Acute Vaginal Candidiasis

| Recommended treatment regimens   | Caution   |
|--|---|
| <ul style="list-style-type: none"><li>- Fluconazole 150-200 mg orally single dose</li><li>- Itraconazole 200 mg orally twice daily for 1 day</li><li>- Clotrimazole 500 mg vaginal suppository single dose</li><li>- Clotrimazole 200 mg vaginal suppository daily for 3 days</li><li>- Clotrimazole 100 mg vaginal suppository daily for 6-7 days</li><li>- Miconazole 100 mg vaginal suppository daily for 7 days</li><li>- Miconazole 200 mg vaginal suppository daily for 3 days</li></ul> | Pregnant women with vaginal candidiasis cannot take oral medications because fluconazole is a pregnancy category C. There was a report showing an association between congenital heart defect and maternal intake of fluconazole 400-800mg/d during the first trimester <sup>(31)</sup> . |

Notes:     - Putting gentian violet in the vagina will help the early improvement of the vaginal itching.  
          - Nystatin 100 000 units (Gynecon®) vaginal suppositories for 14 days or dequalinium chloride 10 mg vaginal suppositories for 6 days are alternative regimens for azole-resistant individuals.  
          - Sertaconazole 300mg is available in Thailand and has an acceptable efficacy.  
Reference: Royal Thai College of Obstetricians and Gynaecologists<sup>(24)</sup>

The azole group, comprising imidazoles (clotrimazole, miconazole, ketoconazole, sertaconazole, econazole) and triazoles (itraconazole, fluconazole), functions by inhibiting 14 $\alpha$ -sterol-demethylase. The production of ergosterol, a vital component of the plasma membrane of *Candida* spp., is thereby reduced. This inhibition results in cell death. Triazoles, which minimally affect sterol synthesis in other body parts, can be administered orally. However, they may present cytochrome P450-dependent enzyme side effects such as vomiting, liver enzyme abnormalities, and QT prolongation<sup>(33)</sup>. Miconazole also operates by augmenting reactive oxygen species within cells, thus enhancing the fungicidal activity of miconazole compared to other drugs<sup>(34)</sup>. The predominant mechanism of drug resistance is mutations in ERG11, the gene coding for 14 $\alpha$ -sterol-demethylase<sup>(33)</sup>.

Nystatin, a polyene, binds directly to ergosterol, triggering plasma membrane perforation, cytoplasmic leakage, acidification, cell lysis, and ultimately cell

death. Potential side effects are rash, localized pain, and itching<sup>(35)</sup>. In Thailand, combination drugs such as nystatin 100 000 IU + diiodohydroxyquinoline 100 mg + benzalkonium chloride 7 mg (brand name: Gynecon®) are available. Gynecon® is packaged in a 7 once-daily-tablet box, which can be used as the primary treatment. However, the antiseptic drugs being combined cause local irritation resulting in their lower popularity. Two boxes of Gynecon® are recommended for those who fail many azole regimens or are suspicious of azole resistance. The long regimen of 14 days can be interrupted by the menstrual period.

Dequalinium chloride, a quaternary ammonium salt, demonstrates antimicrobial and antimycotic activity by increasing cell permeability, leading to a loss of mitochondrial ATP synthesis<sup>(36)</sup>. Its multipurpose may fit health professionals who are not keen on wet preparation. Nonetheless, follow-up must not be neglected. A study on Thai women reported that the treatment efficacy of dequalinium chloride was non-

significantly inferior to that of clotrimazole<sup>(37)</sup>.

The adjunct treatment using topical gentian violet is also recommended as it significantly lessen time-to-cure<sup>(3)</sup>. Gentian violet is a permanently stained violet solution. It has been used to treat both skin and mucosa fungal infections in both children and adults. One mL of gentian violet is pushed into the vaginal cavity during pelvic examination, preferably after removal of curd-like discharge. A sanitation napkin should always be provided after this application. In addition, all patients must be informed that violet vaginal discharge will be evident for a few more days without serious side effects.

## Patient Guidance

Health professionals must ensure that patients comprehend the nature of their ailment, its causes, the prescribed treatment, and necessary self-care measures. They must clearly communicate that VC is not a sexually transmitted disease; therefore, treating sexual partners is not advised. Health professionals should encourage patients to adopt long-term self-care strategies to mitigate risks, as the condition predominantly emerges from vaginal imbalance and is often associated with certain behaviors. VC can be managed with oral medications or vaginal suppositories. However, vaginal suppositories may only be suitable for sexually active individuals. Medical providers should always inquire about the patients' experiences and comfort with suppositories. Moreover, oral medications are contraindicated in pregnancy. The Siriraj Female

Sexually Transmitted Infections Clinic has developed educational resources to help patients understand how to use vaginal suppositories properly and maintain overall vaginal health<sup>(38)</sup>.

Other factors, such as certain nutrients and stress, are associated with VC. Carbohydrates fuel the vaginal fungus. A survey of sugary drink consumption among Thai women found high consumption rates (=more than five glasses of sugary drink per week) in both a VC group (39.4%) and a healthy group (59.5%). The two groups also reported consuming sweets at least three times a week (61.7% and 71.6%, respectively<sup>(39)</sup>. Individuals with VC are advised to curtail sweet intake, and, if being irresistible, preferably consume a small amount of sugar-rich diet in the morning or before physical activity. Screening for diabetes at suitable intervals is also advised. Additionally, evidence suggests that iron deficiency can increase the risk of VC<sup>(9)</sup>. Hence, iron supplementation is often prescribed for symptomatic patients, particularly those with frequent episodes of VC.

## Treatment Experience at the Siriraj Female Sexually Transmitted Infections Clinic

Our attending physicians customize medication protocols in clinical practice based on their experience, often in conjunction with guidance involving other drugs or medical supplies. Their experiences using various drug regimens among nonpregnant women are consolidated in Tables 2.

**Table 2.** Therapeutic Strategies for Acute Vaginal Candidiasis in Nonpregnant Women.

|                          | FLU 1<br>(n=90) | FLU 1,4<br>(n=48) | FLU 1,4,7<br>(n=47) | FLU+CLO<br>cream<br>(n=37) | FLU+SER<br>(n=48) | SER<br>(n=17) | CLO <sup>1</sup> 500<br>(n=25) | CLO <sup>2</sup> 500<br>(n=14) | CLO 100<br>(n=25) | NPF<br>(n=24) | FLU+<br>Fluomizin<br>(n=24) |
|--------------------------|-----------------|-------------------|---------------------|----------------------------|-------------------|---------------|--------------------------------|--------------------------------|-------------------|---------------|-----------------------------|
| Age (years)              | 32.9±8.6        | 33±9.1            | 31.6±8.9            | 34.1±9.6                   | 33±9.1            | 33.1±10.8     | 31.5±10.6                      | 32±9.2                         | 33.6±8.2          | 32.3±9.7      | 30.9±8.7                    |
| BMI (kg/m <sup>2</sup> ) | 23.1±4.3        | 22.7±4.9          | 22.7±4.9            | 21.8±6.4                   | 22.7±4.9          | 22.6±4.0      | 24.7±4.7                       | 22.2±4.4                       | 23.5±4.7          | 20.8±2.5      | 23.2±5.4                    |
| Clinical cure            | 67 (74.4)       | 36 (75.0)         | 32 (68.1)           | 24 (64.9)                  | 36 (75.0)         | 15 (88.2)     | 18 (72.0)                      | 11 (78.6)                      | 16 (64)           | 19 (79.2)     | 18 (75)                     |
| Microscopic cure         | –               | 44 (91.7)         | 39 (83.0)           | 31 (83.8)                  | 44 (91.7)         | 14 (82.4)     | 16 (64)                        | 12 (85.7)                      | 19 (82.6)         | 20 (83.3)     | 22 (91.7)                   |
| Time-to-cure (days)      | 4.0±1.8         | 2.9±2.0           | 2.2±0.6             | 3.3±2.2                    | 2.9±2.0           | 3.7±3.0       | 2.7±1.3                        | 3.8±2.6                        | 2.3±2.8           | 3.2±2.4       | 2.1±2.5                     |

CLO= clotrimazole, FLU=fluconazole, NPF=Neo-Penotrans Forte, SER=sertaconazole

FLU1 =a single dose fluconazole 200mg; FLU 1,4=fluconazole 200mg on first and fourth day; FLU 1,4,7= fluconazole 200mg on first, fourth and seventh day, CLO1= original clotrimazole (Bayer, Thailand); CLO2=generic 500mg clotrimazole (Kenet, Patar Lab (2517), Thailand); SER= sertaconazole 300mg (Pacific Health Care, Thailand)

Source: Unit of Infectious Diseases, Department of Obstetrics and Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University

## ***Treatment of Acute Vaginal Candidiasis in Nonpregnant Women***

A previous study conducted at the Clinic found that the therapeutic efficacy of a single dose of fluconazole 200 mg taken orally was 74.4%. The average onset of symptomatic improvement occurred approximately 4 days post-treatment initiation<sup>(3)</sup>. Since 2020, 309 individuals were treated for acute VC. All presented with abnormal vaginal discharge, with 76.3% reporting itching, 37.3% experiencing foul-smelling discharge during the preceding month, and 5.7% having concurrent fungal infections elsewhere on the body. Among the cohort, 58.6% consumed at least 5 glasses of sweetened beverages per week. The vast majority (89.6%) had experienced abnormal vaginal discharge during the previous year, with 36.8% and 42.8% having symptoms once and twice, respectively. Furthermore, 98% were sexually active, 44.1% used sanitary napkins outside the menstrual cycle, 88.8% used specialized genital cleaning products, 78.2% had a history of vaginal douching, and 65.7% utilized tampons.

In light of expert recommendations which suggest that augmented drug regimens expedite patient recovery and bolster treatment efficacy<sup>(10)</sup>, the Clinic has expanded its drug protocols. Per symptomatic and microscopic evaluations, the clinical cure and microscopic cure of oral fluconazole 200 mg on the first and fourth days were 75% and 91.7%, respectively. However, when the regimen was expanded to 600 mg (3 capsules) and administered on the first, fourth, and seventh days, there was a decline in treatment efficacy. Unlike the study by Quereux et al in which the addition of azole cream increased the cure rate<sup>(40)</sup>, combining oral fluconazole 200 mg and topical clotrimazole cream did not improve outcomes. Conversely, combining fluconazole 200 mg with sertaconazole suppositories enhanced treatment efficacy and hastened symptom resolution, paralleling results observed with 2 doses of fluconazole. Among all treatments, suppositories, especially those containing sertaconazole, proved highly effective, leading to symptom resolution in 88.2% of cases.

Vaginal clotrimazole suppository has been used to treat women with VC for around 50 years and has shown high treatment efficacy and the most acceptable safety<sup>(41)</sup>. When comparing the original clotrimazole (Canesten®, Bayer, Thailand) in the form of single dose and multiple doses, we found that multiple doses led to a lower clinical cure but higher microscopic cure. The local-made clotrimazole had good performance in treatment outcomes that were comparable to the original one. All of the single-dose clotrimazole suppositories being used in the Clinic were applied by residents or experienced gynaecologists in order to minimize inappropriate insertion technique. Accordingly, our findings are applicable for patients who are well-trained for vaginal suppository before the prescription.

The optimal follow-up time is two weeks because, based on our experience, many women become asymptomatic at the end of the first week and start to develop symptoms after that. Normally, patients' symptoms should be at least 50% subsided in the first week and become absent at the end of two weeks. Recurrence mostly occurs within two months post-treatment, in particular those who refuse lifestyle modification. When any participant fails the first regimen, the alternative regimens will be administered. However, drug compliance should be the first issue of concern. Inability to perform vaginal insertion is not an uncommon condition. Therefore, our third-line regimen is usually a two or three doses of fluconazole 200 mg being given in a three-day interval.

## ***Treatment of Acute Vaginal Candidiasis in Pregnant Women***

For pregnant women, vaginal suppositories remain the sole viable treatment modality. Most treatment guidelines recommend the use of suppositories over multiple days<sup>(9)</sup>. However, pregnant women often find suppository administration challenging due to their enlarged abdomen and constraints against lying supine. Our Clinic has therefore documented the therapeutic effects of various regimens. They are a single dose of

clotrimazole 500 mg vaginal suppository, a single dose of sertaconazole 300 mg vaginal suppository, and the daily administration over 7 days of a combination of metronidazole 750 mg with miconazole 200 mg vaginal suppositories (brand name: Neo-Penotran Forte®). Two weeks after treatment, symptomatic improvement was found in 50% (24/48), 62.5% (30/48), and 83.7% (31/43) of the patients for each regimen, respectively. Regarding microscopic cures, the corresponding rates were 62.5% (30/48, 47.9% (23/48), and 72.1% (31/43) of the patients. Satisfaction with treatment outcomes was high across all groups. In order to lessen drug administration and gain prolonged treatment effects, an on-going trial in the Clinic is to compare a single dose of sertaconazole 300mg and two doses of seven-day-interval sertaconazole 300mg.

A small drawback of Neo-Penotran Forte usage is vaginal irritation. Of the patients, 27% experienced symptoms during the initial 1–2 days, 11% had persisting symptoms up to days 3–4, and 8% reported symptoms lasting beyond 4 days. However, all patients were able to complete the treatment regimen. The use of lubricants can mitigate symptoms. In accordance with a previous study in Russian pregnant women that an additional dose of sertaconazole 300mg at a seven-day interval increased cure rate<sup>(41)</sup>, in cases where symptoms persist or fungi are still detectable microscopically, the Clinic recommends adding therapeutic drugs. If initiated with a single vaginal suppository, treatment should be repeated weekly with microbial and symptomatic evaluations

every 2–4 weeks until resolution. Despite being asymptomatic, 1 patient consistently exhibited fungal presence upon microscopic evaluation at each follow-up. Consequently, the Clinic recommends continuing weekly vaginal suppository administration of a single-dose azole regimen for the duration of the pregnancy in case of no treatment response following the third regimen.

### **Chronic Vaginal Candidiasis and Recurrent Episode**

Treatment outcomes of VC can be divided into being cured, being not cured, chronic VC and recurrent VC<sup>(9)</sup>. Chronic VC is a subset of being not cured in that women who belong to chronic VC have no response to many consecutive treatment regimens. In contrast, recurrent VC is a subset of being cured, but there are at least three following VC episodes in 12 months. Since 2020 that we started to set up the follow-up protocol for all women presenting with VC, we telephoned them for asking about their symptoms and recurrent episodes.

Table 3 shows that, among those who could be contacted, recurrent episodes in two years were not common. Health education on lifestyle modification and disease awareness, which is the strength of the Siriraj Female STI Clinic, may be the best explanation. Therefore, we encourage healthcare professionals to focus on this part, not less than the antimycotic one. Furthermore, our findings support the high impact of VC for pregnant women as it was seen that many of them tended to have chronic VC.

**Table 3.** Thai women presenting with acute vaginal candidiasis; being treated with a single dose vaginal suppository; and being followed up to two years

|                                | Being non-pregnant during diagnosis (n=18) | Diagnosis during first trimester (n=7) | Diagnosis during second trimester(n=25) | Diagnosis during third trimester(n=6) |
|--------------------------------|--|--|---|---------------------------------------|
| Microscope cure at 2 weeks     | 15 (83.3)                                  | 3 (42.9)                               | 13 (52)                                 | 4 (66.7)                              |
| No microscopic cure at 2 weeks | 3 (16.7)                                   | 4 (57.1)                               | 12 (48)                                 | 2 (33.3)                              |
| Chronic VC*                    | 0 (0)                                      | 3/4 (75)                               | 6/12 (50)                               | 2/2 (100)                             |
| Recurrence** in 2 years        | 1 (5.6)                                    | 0                                      | 4 (16)                                  | 0 (0)                                 |

Data presented in n(%)

\*Chronic VC = women who had no microscopic cure at 2 week follow-up; and received second single dose, anti-fungal, vaginal suppository; and still had no microscopic cure at the following two weeks. \*\*Recurrence = At least one recurrent episodes being evaluated by telephone call

Source: Unit of Infectious Diseases, Department of Obstetrics and Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University

## Managing Cases with Fungal Detection in Cervical Cancer Screening Results

Cervical cancer screening, particularly cytological examination, often detects *Candida* spp. in the form of yeast or pseudohyphae. *C. albicans* is the most frequently identified pathogen and is often present in pseudohyphae form during the symptomatic period.

A review of cervical cancer test results from 82 patients presenting with acute vaginal candidiasis at the Clinic between June 2020 and May 2021 revealed that approximately 30% had evidence of a fungal infection in their latest Pap test. Intriguingly, these patients did not display typical curd-like vaginal discharge or complain of itching on the testing day. As a result, from June 2022, cervical cancer test reports sent to patients have been updated to indicate the presence of fungus, urging those identified to seek further examination.

Data from 56 individuals with detection of fungus in their latest, they came to the Clinic for pelvic examination ranging from 2 weeks to 2 months. Pseudohyphae were detected microscopically in 30.4% (17/56) of these patients, and 47.1% (8/17) reporting vaginal itching on the day of their consultation. Conversely, 62.5% (35/56) did not exhibit pseudohyphae under microscopic examination, yet 17.7% (6/35) of this group reported vaginal itching and received appropriate treatment. Four cases (7.1%) had self-medicated prior to consultation due to the discomfort from vaginal itching. This observation underscores the importance of follow-up examinations for enhancing diagnostic accuracy; and probably alleviates client anxiety.

## Conclusions

Vaginal candidiasis, resulting from a vaginal imbalance, is prevalent. The dissemination of information on proper healthcare practices is vital to prevent the condition. When symptoms manifest, multiple treatment options are available. Physicians should assess each patient's circumstances, monitor their treatment progress, and provide comprehensive

information regarding the limitations and efficacy of each drug. It is also crucial to address the issue of frequent recurrence and to emphasize the importance of adhering to the prescribed medication regimen to mitigate the risk of drug resistance. Patients should be encouraged to seek medical attention if they are uncertain of their symptoms or abnormal Pap test, given the propensity for this condition to cooccur with other infections.

## References

1. Chayachinda C, Chinchiran K, Kittiyaowamarn R, Chaithongwongwatthana S, Teeratakulpisarn N. The Thai 2022 sexually transmitted infections treatment guideline: abnormal vaginal discharge. *Thai J Obstet Gynaecol* 2022;30:222-33.
2. Chayachinda C, Thamkhantho M, Chalermchokcharoenkit A, Neungton C, Thipmontree W. Characteristics of clients at the Siriraj Female STD Clinic during 2011-2015. *Siriraj Med Bull* 2018;11:182-9.
3. Chayachinda C, Thamkhantho M, Ngamsakulringroj P, Leeyaphan C, Tulyaprawat O. Effect of intravaginal gentian violet for acute vaginal candidiasis treated with a single dose oral fluconazole: a randomised controlled trial. *J Obstet Gynaecol* 2022;7:1-7.
4. Roberts C, Algert C, Rickard K, Morris J. Treatment of vaginal candidiasis for the prevention of preterm birth: a systematic review and meta-analysis. *Syst Rev* 2015;4:31.
5. Blomberg L, Backman K, Kirjavainen P, Karvonen A, Harju M, Keski-Nisula L. Vulvovaginal yeast infections, gestational diabetes and pregnancy outcome. *BMC Pregnancy Childbirth* 2023;23:70.
6. Sobel JD. Vulvovaginal candidosis. *Lancet* 2007;369:1961-71.
7. Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. *BMJ* 2004;329:371.
8. Roberts C, Rickard K, Kotsiou G, Morris J. Treatment of asymptomatic vaginal candidiasis in pregnancy to prevent preterm birth: an open-label pilot randomized controlled trial. *BMC Pregnancy Childbirth* 2011;11:18.
9. British Association for Sexual Health and HIV. British Association for Sexual Health and HIV national guideline for the management of vulvovaginal candidiasis (2019) 2019 28 July 2020. Available from: <https://www.bashhguidelines.org/media/1223/vvc-2019.pdf>.

10. Chalermchockcharoenkit A. (24 August 2022) A novel topical alternative treatment for treating women with acute vaginal candidiasis: Sertaconazole 300 mg [Webinar]. Pacific Health Care, Thailand.
11. Garcia-Rubio R, de Oliveira HC, Rivera J, Trevijano-Contador N. The fungal cell wall: Candida, Cryptococcus, and Aspergillus Species. *Front Microbiol* 2020;10:1-13.
12. Lv Q, Yan L, Jiang Y. The synthesis, regulation, and functions of sterols in *Candida albicans*: Well-known but still lots to learn. *Virulence* 2016;7:649-59.
13. d'Enfert C, Kaune A, Alaban L, Chakraborty S, Cole N, Delavy M, et al. The impact of the Fungus-Host-Microbiota interplay upon *Candida albicans* infections: current knowledge and new perspectives. *FEMS Microbiol Rev* 2021;45:fuaa060.
14. Amabebe E, Anumba DOC. The Vaginal Microenvironment: The physiologic role of Lactobacilli. *Front Med (Lausanne)* 2018;5:181.
15. King R, Lee J, Morris A. Adherence of *Candida albicans* and other *Candida* species to mucosal epithelial cells. *Infect Immun* 1980;27:667-74.
16. Ferrer J. Vaginal candidosis: epidemiological and etiological factors. *Int J Gynaecol Obstet* 2000;71:S21-7.
17. Narayanan T, Rao G. Beta-indoleethanol and beta-indolelactic acid production by *Candida* species: their antibacterial and autoantibiotic action. *Antimicrob Agents Chemother* 1976;9:375-80.
18. Heng L, Yatsuya H, Morita S, Sakamoto J. Vaginal douching in Cambodian women: its prevalence and association with vaginal candidiasis. *J Epidemiol* 2010;20:70-6.
19. Shaaban O, Abbas A, Moharram A, Farhan M, Hassanen I. Does vaginal douching affect the type of candidal vulvovaginal infection? *Med Mycol* 2015;53:817-27.
20. Rachapromma P, Chayachinda C, Kerdklinhom C, Iamvijarn W, Thanasakthitiku T. Nursing care for women with acute vaginal candidiasis. *Siriraj Med Bull* 2022;15: 107-13.
21. Elegbe I, Elegbe I. Quantitative relationships of *Candida albicans* infections and dressing patterns in Nigerian women. *Am J Public Health*. 1983;73: 450-2.
22. Padgett DA, Glaser R. How stress influences the immune response. *Trends Immunol* 2003;24:444-8.
23. Chayachinda C, Rekhawasin T, Thamkhantho M, Aneklap P. Acute vaginal candidiasis: A review of treatment guidelines and Siriraj experience. *Thai J Obstet Gynaecol* 2021;29:306-12.
24. Royal Thai College of Obstetrics and Gynaecologists. Management of abnormal vaginal discharge in reproductive-aged women. *Siriraj Med Bull* 2023;16:187-29.
25. Tuangrattanasirikun D, Chayachinda C, Rachapromma P, Sonwicha S. Effect of on-line vs on-site class on medical students' competency in vaginal wet mount. *Siriraj Med Bull* 2023;16:269-75.
26. Woelber L, Prieske K, Mendling W, Schmalfeldt B, Tietz H, Jaeger A. Vulvar pruritus-causes, diagnosis and therapeutic approach. *Dtsch Arztebl Int* 2020;116:126-33.
27. Chayachinda C, Panchalee T, Thamkhantho M. A Never-ending story of anogenital warts: review article. *J Med Assoc Thai* 2020;103:614-9.
28. Qi W, Li H, Wang C, Li H, Zhang B, Dong M, et al. Recent advances in presentation, diagnosis and treatment for mixed vaginitis. *Front Cell Infect Microbiol* 2021;11:759795.
29. Olson M, Jayaraman A, Kao K. Relative abundances of *Candida albicans* and *Candida glabrata* in in vitro coculture biofilms impact biofilm structure and formation. *Appl Environ Microbiol* 2018;84: e02769-17.
30. Workowski K, Bachmann L, Chan P, Johnston C, Muzny C, Park I, et al. Sexually transmitted infections treatment guidelines 2021. *MMWR Recomm Rep* 2021;70:1-187.
31. Budani M, Fensore S, Di Marzio M, Tiboni G. Maternal use of fluconazole and congenital malformations in the progeny: A meta-analysis of the literature. *Reprod Toxicol* 2021;100:42-51.
32. Ghannoum M, Rice L. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. *Clin Microbiol Rev* 1999;12:501-17.
33. Regidor P, Thamkhantho M, Chayachinda C, Palacios S. Miconazole for the treatment of vulvovaginal candidiasis. In vitro, in vivo and clinical results. Review of the literature. *J Obstet Gynaecol* 2023;43:2195001.
34. Fan S, Liu X, Wu C, Xu L, Li J. Vaginal nystatin versus oral fluconazole for the treatment for recurrent vulvovaginal candidiasis. *Mycopathologia* 2015;179:95-101.
35. Merianoss J. Quaternary ammonium antimicrobial compounds. In: Block S, editor. *Disinfection, sterilization, and preservation*. Fourth ed. Philadelphia: Lea and Febiger; 1991. p. 225-55.
36. Thamkhantho M, Chayachinda C. Vaginal tablets of dequalinium chloride 10 mg versus clotrimazole 100 mg for vaginal candidiasis: a double-blind, randomized study. *Arch Gynecol Obstet* 2021;303:151-60.

37. Chayachinda C, Chinhiran K, Aneklap P, Rachapromma P, Sornwicha S. Bacterial Vaginosis: a comprehensive approach to management in reproductive-aged women. *Thai J Obstet Gynaecol* 2023;31:318-25
38. Hosiriphon K, Chayachinda C, Keawpoonsub K, Taibowornpitak K, Tuangrattanasirikun D. A Survey of daily genital care practices among reproductive-aged female personnel at Siriraj Hospital. *Siriraj Med J* 2023;75:259-65
39. Quereux C, Gelas B, Chevallier T, Petit F, Micheletti M. Evaluation of the efficacy and speed of action of sertaconazole nitrate suppository and cream combined treatment for vulvovaginal candidiasis. *Gynecol Obstet Fertil* 2000;28:238-44.
40. Mendling W, Atef El Shazly M, Zhang L. Clotrimazole for vulvovaginal candidiasis: more than 45 years of clinical experience. *Pharmaceuticals* 2020;13:274.
41. Egorova AT, Bazina MI, Savitskaya EA. The experience of treatment of Candida vulvovaginitis in pregnant women with 'Zalain'. *Russian Bulletin of Obstetrician-Gynaecologist* 2010;4:35-8.