

BASHH



British Association for Sexual Health and HIV national guideline for the management of vulvovaginal candidiasis (2019)

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NEW IN THE 2019 GUIDELINES

Terminology:

- The new guidelines refer to 'acute' and 'recurrent' vulvovaginal candidiasis (VVC) and no longer use the terms 'uncomplicated' and 'complicated' VVC; the new definitions are felt to be more reflective of how women with VVC typically present to clinical services and are subsequently managed
- The elements of complicated VVC where single dose treatments are not always appropriate are still covered within the guideline under the relevant sections

Diagnosis:

- Microscopy is the primary laboratory investigation for acute VVC; culture is no longer recommended as a primary laboratory investigation for acute VVC
- Culture is still recommended for recurrent VVC with appropriate speciation and sensitivity testing depending on clinical indication
- Greater emphasis has been placed on ensuring that other vulval pathologies are not missed in the setting of possible recurrent VVC
- Interpretation of antifungal susceptibility testing should take into account the acid pH of the vagina compared with the neutral pH at which testing is usually performed; the activity of azole antifungals is reduced in acidic environment and clinical resistance may occur despite the isolate being microbiologically susceptible.

Treatment:

- Oral azoles – continue to avoid in pregnancy, at risk of pregnancy and whilst breastfeeding
- Ketoconazole is no longer recommended for the treatment of VVC
- Non-azole therapies to be reserved for azole resistance and certain non-albicans *Candida* species

INTRODUCTION AND METHODOLOGY

Objectives

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles for the effective management of vulvovaginal candidiasis (VVC). It covers the management of acute and recurrent VVC.

It is aimed at individuals aged 16 years and older (see specific guideline for under 16 year olds) presenting to healthcare professionals working in departments offering level 3 care in sexually transmitted infections (STIs) management within the UK.

However, the principles of the recommendations can be applied in other settings using local care pathways where appropriate. Guidelines for the management of vaginal discharge in non-genitourinary medicine settings can be found at:

<https://www.bashhguidelines.org/media/1089/sexually-transmitted-infections-in-primary-care-2013.pdf>.

Search strategy

This document was produced in accordance with the guidance set out in the CEG's document 'Framework for guideline development and assessment' at <http://www.bashh.org/guidelines>. The GRADE system was used to assess the evidence and make recommendations as detailed in the guidance.

The following reference sources were used to provide a comprehensive basis for the guideline:

1. Medline, Embase, Cochrane and CINAHL Search
 - a. January 2007-August 2016⁺
 - b. The search strategy comprised the following terms in the title or abstract: [Vagina* OR vulva* OR vulvovaginal OR vulvo-vaginal OR vaginosis OR vaginitis OR vulvitis OR thrush (NOT oral)] AND [Candida OR candidiasis OR candidosis OR yeast]. The search was limited to English language and human subjects. 1412 citations were identified.
2. 2007 UK National Guidelines on the Management of Vulvovaginal Candidiasis.

⁺ The search period was extended to March 2018 during the peer review of first draft of the guideline to identify any new relevant evidence.

Methods

- The broad search terms used above were necessary given the various international terminology used for VVC but resulted in a large number of citations (1412).

- The article titles and abstracts of all 1412 citations were reviewed for relevance. Citations clearly from animal studies, non-patient based studies, single case reports, studies in children, and those on subjects not relevant to the diagnosis or management of VVC were excluded on first review.
- The titles and abstracts of the remaining citations (800) were reviewed by at least two members of the writing group. Priority was given to randomised controlled trials, systematic review evidence, and studies related to pertinent clinical questions to be addressed by the guideline.
- The full texts of approximately 210 citations were obtained and reviewed using the GRADE system by at least two members of the writing group. Recommendations were made and graded on the basis of best available evidence.

Equality impact assessment

See appendix 1

Piloting & feedback

The first draft was produced by the writing group and then circulated to BASHH CEG for using the AGREE appraisal tool. The second draft of the guideline is posted on BASHH website for wider consultation and simultaneously reviewed by the BASHH Public Panel. The final draft will be presented to the CEG for review and piloting in their clinics.

Once the guideline is published to the BASHH website the CEG will keep it under review should critical new evidence become available that affects the current recommendations. The guideline will be formally reviewed and updated every 5 years.

DEFINITIONS

Acute VVC

- First or single isolated presentation of vulvovaginal candidiasis (VVC)
- Patients typically present with signs and symptoms of acute vulvovaginitis and *Candida sp.* can be detected by microscopy and/or culture.

Recurrent VVC

- At least 4 episodes per 12 months with 2 episodes confirmed by microscopy or culture when symptomatic (at least one must be culture)
- Patients with recurrent VVC typically fall into one of two groups depending on response to therapy with implications for diagnosis and management:
 - **good or complete response to therapy** and asymptomatic between episodes, or
 - **poor or partial response to therapy** with persistence of symptoms between treatments.

AETIOLOGY

Candidiasis is a fungal infection caused by yeasts that belong to the genus *Candida*. Yeasts are eukaryotic, unicellular microorganisms which have the ability to develop multicellular characteristics by forming pseudohyphae and biofilms. *Candida* yeasts are present in low numbers on healthy skin in moist areas and are part of the normal flora of the mucous membranes of the respiratory, gastrointestinal and female genital tracts; overgrowth of these organisms can cause infection to develop. There are over 20 *Candida* species that can cause infections in humans, of which *Candida albicans* is the most common. *Candida* can also cause serious systemic infections, but these do not originate from genital tract infections.

Vulvovaginal candidiasis (VVC) is caused by:

- *Candida albicans* in 80-89%¹⁻³
- Other *Candida* species or yeasts such as *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. parapsilosis*, and *Saccharomyces cerevisiae* in the remainder.

Despite the widespread availability of antifungal agents in the UK clinical resistance remains rare. There is no surveillance data on azole susceptibility of VVC isolates in the UK but there are reports of decreased susceptibility and clinical resistance from elsewhere including China and other countries and settings with very high levels of azole use.^{2,4-7} There is no evidence for emergence of non-albicans *Candida* species inherently resistant to azoles.^{3,8} There remains conflicting evidence on the virulence and pathogenicity of non-albicans *Candida* species compared with *C. albicans*.^{9,10}

An estimated 75% of women will have at least one lifetime episode of VVC, and 40–45% will have two or more episodes.¹¹ Previous studies have reported that approximately 6% of women of reproductive age will develop recurrent disease.^{12,13} A large internet-based survey across five European countries (including the UK) and the US found that over 20% of women reporting at least one episode of vaginal yeast infection also reported a 12-month period with four or more infections. The probability of developing recurrent VVC after an initial infection was 10% by the age of 25 years and 25% by the age of 50 years.¹⁴

Risk factors and pathogenesis

Recurrent VVC is thought to be related to host factors rather than more virulent strains or reintroduction of the organism to the genital tract. The majority are usually due to *C. albicans*.¹⁵ For many women an identifiable host factor is not found but can include:

- persistence of *Candida sp* (as detected by PCR although culture-negative between attacks)¹⁶
- poorly controlled diabetes mellitus
- immunosuppression
- endogenous and exogenous oestrogen (including pregnancy, HRT and possibly the combined oral contraceptive pill)¹⁷⁻²⁰
- recent (up to three months before the episodes) antibiotic use causing a disturbance in the vaginal flora.^{17,21,22}

On other mucous membranes IL-17 mediated immune responses may be crucial, but this may not be the case in the vagina.²³ Symptoms of VVC are correlated with fungal burden and neutrophil infiltration is involved with symptom production.^{24,25} This may relate to the identified link to allergy (allergic rhinitis, asthma and hay fever)^{19,26} and pro-inflammatory genetic markers. However, women suffering from allergic diseases are more likely to have used corticosteroids, so it is unclear as to whether the steroid use, or concomitant atopic disease makes them more susceptible.¹⁹ Perceived increased stress and a lower mean

cortisol (which may correspond to chronic stress) have been weakly associated with recurrent VVC however the evidence is limited, and further research is required.^{27, 28}

It is unclear if iron deficiency anaemia is associated with recurrent VVC. A previous study found no evidence of low iron levels in women with VVC²⁹ however a more recent study suggests a possible link between iron deficiency anaemia and recurrent VVC.³⁰ The earlier study reported statistically significant lower serum level of zinc, magnesium and calcium in patients with recurrent VVC, although all levels were still within the normal range; other studies have not supported the link with serum zinc levels.^{29, 31}

Mannose binding lectin (MBL) deficiency is a genetic condition that affects the immune system. Several studies have shown that MBL codon 54 gene polymorphism is associated with recurrent and acute VVC. In particular, possessing the MBL variant allele B heterozygous genotype increases the susceptibility of women to recurrent or acute VVC compared to healthy controls, while the risk of recurrent VVC is also increased for women carrying the allele B homozygote genotype.³²⁻³⁴

CLINICAL FEATURES

Vulvovaginal candidiasis (VVC) typically presents with:³⁵⁻³⁹

- vulval itch and
- a non-offensive vaginal discharge.

Other symptoms can include:^{35, 38-40}

- soreness or burning
- superficial dyspareunia
- cyclical symptoms.

Clinical signs may include:³⁵⁻⁴⁰

- erythema
- fissuring
- swelling/oedema

- vaginal discharge typically non-offensive and curdy but may be thin or absent
- there may also be satellite lesions and excoriation marks.

None of these features are pathognomonic for VVC and there can be a significant discrepancy between symptoms and signs particularly in chronic disease.^{40, 41} Although *Candida albicans* is the most pathogenic of the *Candida* species clinical symptoms or signs cannot be used to guide which *Candida sp* is the cause for the infection.^{41, 42} Health-related quality of life both physical and psychological is significantly affected in recurrent VVC.³⁸

In women with recurrent VVC enquiry about other recurrent infections, particularly those suggestive of fungal infection (e.g. oropharyngeal, skin, nails, dandruff) is relevant. Rarely, the history may indicate an immune defect and the need for referral to immunology for assessment.⁴³

Differential diagnoses and colonisation

- Many women (more than half of self-diagnosed women in one study⁴⁴) presenting with these symptoms may have other conditions such as:
 - dermatitis/eczema
 - lichen sclerosus
 - other infections (such as herpes simplex, trichomonas vaginalis)
 - vulvodynia
 - aerobic vaginitis
 - cytolytic vaginosis
- The preponderance of certain symptoms and signs, whilst not pathognomonic can be more suggestive of other conditions (table 1 and 2)
- Some women may have dual pathology with VVC and one of these other conditions
- There is a possibility that provoked vestibulodynia is interlinked with VVC and in some women may be triggered by VVC^{45, 46}
- Aerobic vaginitis should be considered if the primary complaint is of a purulent non-offensive discharge⁴⁷
- Cytolytic vaginosis can present with very similar clinical features including curdy discharge and pruritus but microscopy and fungal cultures are negative^{48, 49}
- Up to 20% of women during reproductive years may be colonized with *Candida spp.* but have no clinical signs or symptoms;^{50, 51} these women do not require treatment

- It is also possible that women with vulval symptoms due to other conditions (such as eczema, lichen sclerosus, vulval pain) may have colonisation with *Candida* which is not necessarily contributing to the symptoms.

DIAGNOSIS

- Vulvovaginal candidiasis (VVC) is a clinical diagnosis based on typical features supported by laboratory confirmation of *Candida* sp. from a vaginal sample
- In women presenting with clinical features of acute VVC to a service providing level 3 STI care supporting the diagnosis with routine microscopy is good clinical practice ^{41, 52-57} (Grade 1B) (figure 1)
- Recurrent VVC is defined as four or more symptomatic episodes over a 12-month period; at least two of these episodes should be confirmed by microscopy or culture, one of these should be a positive culture with moderate or heavy growth of *Candida* sp. ⁵⁸⁻⁶¹ (Grade 1C)

Clinical examination and syndromic management

- Clinical examination of the external genitalia is recommended in women presenting with symptoms suggestive of acute VVC in order to exclude alternative or co-existing vulvovaginal pathologies
- Women presenting with features suggesting recurrent VVC should always have a clinical examination ⁶² (Grade 1C)
- Where clinical examination is not possible or required self-collected vaginal swab for microscopy and or culture is a reasonable alternative to clinician taken samples ⁶³ (Grade 1C)
- Empirical treatment for acute VVC based on the reported symptoms may be given in non-specialist settings ⁶⁴; if the symptoms do not resolve, or if they recur, examination and microbiological testing (as below) should be performed. ⁶²

Microscopy

- A high vaginal swab (HVS) of the discharge should be taken for Gram stain and/or phase contrast wet film microscopy
- Presence of blastospores, pseudohyphae and neutrophils is indicative of infection caused by *Candida* species
- Presence of blastospores only and neutrophils may reflect infection caused by *C. glabrata*

- Neutrophils in vaginal secretions suggest an inflammatory response and therefore presence of infection which may or may not be due to *Candida* seen on microscopy. Absence of neutrophils in the presence of *Candida* is likely to represent colonisation.

Culture

Acute VVC:

- Fungal culture is no longer considered a cost-effective addition to microscopy nor a reliable test on its own for the diagnosis of acute VVC due to its inability to differentiate colonisation from infection.

Recurrent VVC:

- An HVS of the discharge should be taken for direct plating onto solid fungal growth medium (Sabouraud plate). The benefit of direct plating is that it enables some level of quantification of *Candida* in the sample.
- If direct plating is not available sending an HVS in a transport medium appropriate for fungal culture is a suitable alternative. However, quantification is not reliable for samples kept in transport medium for more than 12 hours due to continued growth.
- Any fungal growth should ideally be identified to species level, or at least as *C. albicans*/non-*albicans Candida*⁵⁸⁻⁶¹ (Grade 1B) and sensitivity to fluconazole tested; in cases of recurrent VVC with poor or partial response to therapy, full speciation and sensitivity testing is recommended
- Mixed infection with *C. albicans* and a non-*albicans Candida* species is not rare and should be sought for in the laboratory⁶⁵
- Self-collected swabs done at home can be considered in recurrent VVC where initial samples collected in clinic have come back negative^{66, 67} (Grade 2C)
- For patients reporting poor or partial response to sensitivity guided antifungal therapy a negative post-treatment fungal culture (implying mycological cure) indicates the need to consider alternative or additional diagnoses with similar clinical features (see **Differential Diagnoses** section above).

Interpretation of anti-fungal sensitivity testing

- It is useful to know that standard *in vitro* susceptibility testing for *Candida spp.* is performed at pH 7.0 and that activity of most azole antifungals, particularly those for non-*albicans* species, is significantly decreased in acidic environment.^{68, 69}

- In cases of VVC, the vaginal pH is usually in the range of 4 to 4.5, therefore, isolates with elevated MICs are unlikely to respond to standard doses of azole treatment despite still designated as susceptible:
 - e.g. *C. glabrata* has variable intrinsic resistance to azole antifungals and their marginal efficacy is lost at pH 4.5
- If standard neutral pH is used for susceptibility testing caution is needed when interpreting the results as standard breakpoints may not apply. (Grade 1B)
- The practical implications of this are that reported resistance is likely to predict a poor clinical response, but apparent in vitro sensitivity does not necessarily exclude clinical resistance.

Molecular and point of care testing for VVC

A number of studies have looked at molecular and rapid antigen detection point of care tests for *Candida*.⁷⁰⁻⁷² There are significant differences between the tests and their sensitivity and specificity when compared with the agreed standard of care (microscopy and culture). Some tests are highly sensitive and unable to differentiate between colonisation and infection. Further research and evaluation of cost-effectiveness is required before any recommendations can be made regarding their use in level 3 STI services.

STI screening

VVC is not a sexually transmitted infection (STI) or a marker for STIs. The offer of STI screening should be based on a risk assessment and consideration that some of the clinical features of VVC are similar to those of STIs. For comprehensive guidance on screening for STIs please refer to the 2015 BASHH CEG group guidance on tests for STIs [<https://www.bashhguidelines.org/media/1084/sti-testing-tables-2015-dec-update-4.pdf>].

MANAGEMENT

General advice for all women with VVC symptoms

Patients should be provided with information about the importance of good skin care:

- avoiding the use of local irritants such as perfumed soaps or wipes
- the use of an emollient for personal hygiene as a soap substitute, as a moisturiser and a barrier cream (patient needs to be informed that this does not constitute “internal use”).

Sex does not need to be avoided from an infection perspective as VVC is not a sexually transmitted infection. Women may wish to avoid sex until symptoms have improved particularly if there is fissuring of the skin.

General advice for recurrent VVC

In patients with recurrent VVC careful review of their daily hygiene routine may identify potential local irritants not perceived as such by the patient for example washing hair in bath water or excessive cleaning. (Grade 2D) No other genital hygiene practices have been definitively linked with recurrent VVC however a number have shown weak associations which may be worth considering in certain patients:

- wearing incorrectly fitted clothing made from non-breathable fabric ^{17, 73, 74} (Grade 2C)
- using intermenstrual or daily panty liners ⁷⁴⁻⁷⁷ (Grade 2C)
- vaginal douching ^{22, 74, 78, 79} (Grade 2C)

Vulval emollients may give symptomatic relief as vulval dermatitis (eczema) both primary and secondary is commonly present. ⁸⁰

An association between sexual intercourse and *Candida* colonisation levels or vaginal symptoms has not been identified although there is a paucity of research in this area. ⁸¹ Patients reporting a link between symptoms and sexual activity may wish to consider the use of a gentle water-based lubricant. (Grade 2D) Psychosexual and emotional issues with reduced libido and arousal are common with any chronic vulvovaginal condition and should be discussed.

Further Investigation

No additional investigations are routinely recommended in patients presenting with acute VVC unless clinically indicated. In recurrent VVC screening for the following conditions may be considered particularly if there are additional indicators:

- diabetes with urinalysis, random blood glucose or HbA1c (Grade 2C)
- iron-deficiency anaemia with a full blood count or serum ferritin (Grade 2C)

Screening for mannose binding lectin deficiency can be considered if there are additional clinical indicators (e.g. history of recurrent upper respiratory tract infections or otitis media, autoimmune conditions).⁸² (Grade 2B). Identifying MBL deficiency may help a patient better understand their condition, offer additional reassurance and reduce the need for significant lifestyle changes that can impact on quality of life and are unlikely to improve symptoms.³³ Advice on testing can be sought from your local immunology department or referral to immunology to assess for other immune defects may be more appropriate depending on the history.

TREATMENTS

Acute VVC

Recommended regimen:

- Fluconazole* capsule 150mg as a single dose, orally (1B)

Recommended topical regimen (if oral therapy contraindicated):

- Clotrimazole pessary 500mg as a single dose, intravaginally** (1B)

Alternative regimens:

- Clotrimazole vaginal cream (10%) 5g as a single dose, intravaginally** (1B)
- Clotrimazole pessary 200mg intravaginally at night for 3 consecutive nights** (1C)
- Econazole pessary 150mg intravaginally as a single dose or 150mg intravaginally at night for 3 consecutive nights** (1B)
- Fenticonazole capsule intravaginally as a single dose 600mg or 200mg intravaginally at night for 3 consecutive nights** (1B)
- Itraconazole 200mg orally twice daily for 1 day PO* (1B)
- Miconazole capsule 1200mg intravaginally as a single dose, or 400mg intravaginally at night for 3 consecutive nights** (1B)
- Miconazole vaginal cream (2%) 5g intravaginally at night for 7 consecutive nights** (1B)

Treatment choice:

Studies and data published over the past 10 years on the treatment of acute vulvovaginal candidiasis (VVC) support the treatment regimen recommended in the 2007 guidelines (table 3):

- All intravaginal imidazoles and oral azoles give a clinical and mycological cure rate of over 80% in acute VVC ^{83, 84} (Grade 1B)
- Intravaginal imidazoles and oral azoles are equally effective and tolerable in the management of acute VVC with no difference in treatment outcomes ⁸⁴⁻⁸⁷ (Grade 1B)
- Recommended and alternative regimens have been made for this guideline update based on differences in cost and convenience of dosing (fluconazole 150mg stat PO is 7-30 times cheaper than all other listed regimens; current UK prices February 2019)
- One RCT suggested that a single dose of oral fluconazole may be more effective than prolonged intravaginal clotrimazole 200mg (for 6 days) at clinical cure at 7 days. ⁸⁵ (Grade 1C)

Treatment considerations:

- *Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding ^{51, 73, 84} (Grade 1B); topical imidazoles are a safe and effective alternative in these situations (see 'Pregnancy and Breastfeeding' section below) ^{88, 89}
- **Intravaginal and topical treatments can also damage latex condoms and diaphragms with case reports of unplanned pregnancies ⁸⁵; women must be appropriately counselled about this risk
- As there is minimal absorption of topically applied imidazoles from the vulvovaginal mucosae there is limited risk of systemic side effects
- Topical therapies can cause vulvovaginal irritation and this should be considered if symptoms worsen or persist
- A medication history should be taken to advise women that oral fluconazole and other azoles can interact with medications. In general, fluconazole interactions relate to multiple-dose treatments rather than single-dose use:
 - Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4
 - The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole

- Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram.
- An individual assessment based on additional risk factors is advisable before prescribing two or more drugs associated with QT prolongation (increasing age, female sex, cardiac disease, and some metabolic disturbances (notably hypokalaemia) predispose to QT prolongation)
- Co-administration of medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine and erythromycin are contraindicated in patients receiving fluconazole.

Severe Vulvovaginal Candidiasis

Recommended regimen:

- Fluconazole 150mg orally on day 1 and 4 (1B)

Alternative regimens:

- Clotrimazole 500mg pessary intravaginally on day 1 and 4 (1B)
- Miconazole vaginal capsule 1200mg on day 1 and 4 (1B)

In patients with severe VVC (i.e. extensive vulval erythema, oedema, excoriation, and fissure formation)⁹⁰ regardless of a history of recurrence, fluconazole 150mg should be repeated after three days as this improves symptomatic response but does not influence the risk or rate of recurrence.⁹¹ (Grade 1B) There is no benefit of a seven day topical treatment course over a single oral dose of fluconazole.⁹² If oral treatment is contraindicated it is more logical to repeat a single dose pessary after three days. Two doses of clotrimazole 500mg vaginal tablet or miconazole nitrate vaginal suppository 1,200 mg were as effective as two doses of an oral fluconazole 150 mg regimen in the treatment of patients with severe VVC.^{93, 94} (Grade 1B). Due to significant differences in cost fluconazole is the recommended regimen.

Low-potency corticosteroid creams are also thought by some experts to accelerate symptomatic relief in conjunction with adequate antifungal therapy.⁹⁵ (Grade 2D)

Recurrent VVC

Recommended Regimen:

- **Induction:** fluconazole 150mg orally every 72 hours x 3 doses* (1A)
- **Maintenance:** fluconazole 150mg orally once a week for 6 months* (1A)

Alternative Regimens:

- **Induction:** topical imidazole therapy can be increased to 7-14 days according to symptomatic response (Grade 2C)
- **Maintenance for 6 months:**
 - Clotrimazole pessary 500mg intravaginally once a week (1B)
 - Itraconazole 50-100mg orally daily*(2C)

* Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding^{51, 73, 84} (Grade 1B)

Treatment choice:

The principle of therapy involves an induction regimen to ensure clinical remission, followed immediately by a maintenance regimen

- Fluconazole 150mg every 72 hours for 3 doses followed by 150mg weekly for a six-month period has been shown to have good efficacy and tolerability in two randomized control trials achieving clinical remission in 82-90%⁹⁶ (Grade 1A)
- Fluconazole reduced the frequency of recurrent VVC in 88% immediately after the cessation of therapy, 64% at 3 months after and 61% at 6 months after the end of treatment⁹⁶
- When oral therapy needs to be avoided 500 mg of intravaginal clotrimazole administered weekly may be used as an alternative (Grade 1B)
- There is no evidence for the superiority of itraconazole over fluconazole and microbiological cross-resistance is common whereby it is not likely to be helpful in clinically fluconazole-resistant cases
- Fluconazole is the cheapest oral option for suppression and clotrimazole pessaries the cheapest topical option (current UK prices February 2019)

- If a patient relapses between doses consider twice-weekly Fluconazole 150mg orally; (Grade 2C) alternatively consider the addition of cetirizine 10mg od or an alternative antihistamine particularly if there is a history of allergy⁹⁷
- Evidence does not support the use of low dose protracted regimens such as fluconazole 50mg od for 14-28 days for recurrent VVC and suggests there is potential for development of antifungal resistance⁹⁸
- There is a low risk of idiosyncratic drug-induced hepatitis with oral azoles, although fluconazole is less frequently associated with hepatotoxicity than itraconazole (see later 'Reactions to treatment');
- Oral ketoconazole is no longer recommended for the treatment of fungal infections due to the risk of hepatotoxicity outweighing the potential benefits.⁹⁹

Treatment duration:

There are no trials addressing the optimal duration of suppressive therapy with the majority of trials using 6 months maintenance as standard:

- If recurrences after maintenance regimen are infrequent, each episode should be treated independently
- If recurrent disease is re-established the induction and maintenance regimens should be repeated (Grade 2C)
- One study achieved clinical remission in 90% of women at 6 months and 77% of women at 12 months using an individualized reducing regimen of fluconazole.¹⁰⁰ However it is not clear how this strategy compares to the standard 6 month regimens. A study comparing these strategies is required before recommendations on reducing regimens can be made.

Topical cream:

The role of anogenital persistence of *Candida* and the use of topical creams in recurrent VVC remains unclear. A small uncontrolled case series of 129 women with recurrent VVC found that a combination of oral fluconazole for 20 days and a topical antifungal agent applied to the interlabial sulci of the external vulva and perianally once daily for 4 weeks resulted in a recurrence rate of 34% at 12 months.³⁷ Further research in this area is required before formal recommendations can be made.

Recurrent VVC with poor or partial response to therapy:

It is important to note that patients reporting recurrent episodes or chronic symptoms of VVC with poor or partial response to therapy may have a non-albicans *Candida* species and/or azole resistance (see below). A

sustained resolution of symptoms may be achievable for these patients with the correct treatment following species identification with antifungal sensitivity testing without the need for maintenance treatments. Alternatively they may not have *Candida* or the *Candida* may not be responsible for their symptoms (see 'Differential Diagnoses' section above).

Patients reporting chronic, continuous symptoms, which may improve during menses and remit with antifungal therapy have recently been proposed as having a distinct condition to recurrent VVC referred to as chronic VVC ³⁹: One retrospective study of 208 patients found long-term maintenance regimens of fluconazole or itraconazole were well tolerated in women with chronic VVC (mean duration of follow up 26.2 months; range 5 months to 8.5 years). ¹⁰¹ Further research and study comparing maintenance regimens and durations is required before specific recommendations can be made.

Non-*albicans* *Candida* species and azole resistance

Recommended Regimen:

- Nystatin pessaries 100,000units intravaginally at night for 12-14 consecutive nights (1B)

Alternative Regimens:

- Boric acid vaginal suppositories 600mg daily for 14 days* (1B)
- Amphotericin B vaginal suppositories 50mg once a day for 14 days (2C)
- Flucytosine 5g cream or 1g pessary intravaginally with amphotericin or nystatin daily for 14 days (2C)

*Avoid in pregnancy or risk of pregnancy

Recurrent VVC due to azole resistant *Candida*:

- Nystatin pessaries 100,000units intravaginally at night for 14 nights per month for 6 months (2C)
- Consider 14 days per month for 6 month of the alternative regimens (2D)

Antifungal susceptibility:

- *Candida albicans* is normally susceptible to all yeast-active antifungals although resistance may rarely develop on prolonged or repeated azole treatment courses; resistance to other yeast-active antifungals is very rare
- The most common non-*albicans Candida* species causing vulvovaginitis are *Candida glabrata* and *Candida krusei*:
 - these can be the sole cause of infection or in combination with *C. albicans*
 - most vaginal *C. glabrata* strains are reported as susceptible to azoles¹⁰² but with elevated MICs and often with poor clinical response to standard dose treatment
 - *Candida krusei* is intrinsically resistant to fluconazole¹⁰³
- Some non-*albicans Candida* species such as *C. guilliermondii* and *C. parapsilosis* are normally susceptible to azoles and patients clinically respond to treatment with these
- For an infection caused by an azole resistant *Candida* species longer courses of the non-azole therapy are advised although there is no data on optimum duration; two weeks is suggested
- For isolates with an elevated MIC but still designated susceptible, higher and more frequent dosing of fluconazole may be effective (200-300 mg od every 48 hours for 1 week) but repeated courses should be avoided to prevent further development of resistance.

Treatment options:

- Nystatin preparations are well tolerated and give a 70-90% cure rate in the setting of acute VVC.^{51, 104} They are the only licenced alternative to azole therapy.
- Boric acid vaginal suppositories 600mg daily for 14 days are a safe and effective alternative.^{102, 105, 106} (Grade 1B) If mucosal irritation occurs the dose can be reduced to 300mg daily (additional cost likely as it needs to be compounded specially).¹⁰⁷ There may be a teratogenic risk so boric acid should be avoided in pregnancy or risk of pregnancy.¹⁰⁸
- Amphotericin B vaginal suppositories 50mg once a day for 14 days has a 70% success rate.¹⁰⁹ (Grade 2C)
- Intravaginal flucytosine together with amphotericin or nystatin to reduce the chances of resistance (for which there is a low genetic barrier) can also be used for two weeks.^{8, 102, 110} (Grade 2C)
- There are no studies where the efficacy and tolerability of these drugs has been compared. Where there is reduced sensitivity increasing the dose or combining topical and oral agents may be beneficial.
- Intravaginal and topical treatments can damage latex condoms and diaphragms with case reports of unplanned pregnancies⁸⁵; women must be appropriately counselled about this risk.

Treatment availability:

- Nystatin and boric acid pessaries are both currently (February 2019) available through unlicensed wholesaler specialists but there can be supply issues.
- Although listed as potential alternatives, topical amphotericin B and flucytosine products are not currently available as licensed products through standard UK wholesalers or as imported products via unlicensed wholesaler specialists. At the time of writing (February 2019) they are also not available as a made to order items via an NHS 'specials' manufacturer (Pro-FILE).
- Please contact your local pharmacist for up to date information.

Recurrent VVC due to azole resistant *Candida*:

In patients with recurrent VVC due to fluconazole resistant *Candida* species, 14 days of nystatin pessaries a month for 6 months has been shown to be effective and is more likely to achieve mycological cure than fluconazole regimens.¹¹¹ (Grade 2C) There is no evidence for the treatment protocols for the alternative treatment options but it would seem reasonable to consider extrapolating this suggested regimen of 14 days a month for 6 months to the alternative options. (Grade 2D)

Pregnancy & Breastfeeding

Recommended regimens (acute VVC in pregnancy):

- Clotrimazole pessary 500mg intravaginally at night for up to 7 consecutive nights* (1C)

Alternative regimens (acute VVC in pregnancy):

- Clotrimazole vaginal cream (10%) 5g intravaginally at night for up to 7 consecutive nights* (1C)
- Clotrimazole pessary 200mg intravaginally at night for up to 7 consecutive nights (1C)
- Econazole pessary 150mg intravaginally at night for up to 7 consecutive nights (1C)
- Miconazole capsule 1200mg* or 400mg intravaginally at night for up to 7 consecutive nights (1C)
- Miconazole vaginal cream (2%) 5g intravaginally at night for 7 consecutive nights (1C)

* **Duration of therapy:** longer courses are recommended in pregnancy; a systematic review found that a four day course will cure just over 50% whereas a seven day course cures over 90%.¹¹² (Grade 1B) The studies included in the systematic review used lower dose formulations of topical imidazoles. In theory a full seven day course of the higher dose formulations (clotrimazole 500mg pessary or 10% cream, miconazole 1200mg)

is unlikely to be clinically necessary but there is insufficient evidence to make a more specific recommendation.

Recommended regimen (recurrent VVC in pregnancy):

- **Induction:** topical imidazole therapy can be increased to 10-14 days according to symptomatic response (Grade 2C)
- **Maintenance:** Clotrimazole pessary 500mg intravaginally weekly (1C)

Recommended regimens (acute and recurrent VVC in breastfeeding):

- Treatment regimens using topical imidazoles should be as per the recommendations listed above for non-pregnant women with acute and recurrent VVC.

General considerations:

- Asymptomatic colonisation with *Candida* species is more common (30-40%) ¹¹³ and symptomatic candidiasis is more prevalent throughout pregnancy
- Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding ^{51, 73, 84} (Grade 1B)
- Topical imidazoles are safe and effective for symptomatic VVC in pregnancy and breastfeeding ^{88, 89} (Grade 1B)
- There is no evidence that any one topical imidazole is more effective than another.

Fluconazole in breastfeeding:

- Fluconazole concentrations in breast milk are expected to be very low and unlikely to be harmful
- Breastfeeding can be maintained after a single dose of 150mg Fluconazole but should be avoided after repeated or high doses of fluconazole¹¹⁴
- Topical imidazoles are safe and equally effective alternatives to oral azoles for the management of VVC and therefore the treatment of choice in breastfeeding.

Fluconazole in pregnancy:

- Given the conflicting evidence below, and the fact that topical therapies are equally effective in the management of VVC, we continue to advise against the use of fluconazole and other oral azoles in pregnancy (Grade 1B):
 - A systematic review found that first trimester use of fluconazole does not appear to increase the overall risk of congenital malformation although one study reported a possible link with tetralogy of Fallot ¹¹⁵
 - The United States National Birth Defects Prevention Study (NBDPS) found associations between fluconazole use in the first trimester of pregnancy with cleft lip with cleft palate and d-transposition of the great arteries although overall fluconazole use in the NBDPS was low ¹¹⁶
 - A nationwide register-based cohort study in Denmark (1997-2013) with a cohort of 1,405,500 pregnancies found a statistically significant increased risk of spontaneous abortion in women exposed to fluconazole between 7-22 weeks gestation compared with risk among unexposed women and women with topical imidazole exposure in pregnancy ⁸⁸
 - A preliminary study in Denmark with 812 mother-son pairs found that fluconazole exposure in 4 pregnant women was significantly associated with shorter anogenital distance suggesting a potential anti-androgenic effect. ¹¹⁷
- It is important to note that exposure to standard dose fluconazole at any stage in pregnancy would not usually be regarded as medical grounds for termination of pregnancy or any additional foetal monitoring.

¹¹⁸

VVC and pregnancy outcome:

- Previous studies did not find evidence of an association between *Candida* colonisation and premature delivery or low birth weight. ^{113, 119}
- There remains insufficient evidence of an association between detecting asymptomatic VVC in pregnancy and the risk of pre-term birth or low birth weight ¹²⁰⁻¹²⁵; well-designed studies in this area are warranted.

Alternative or Supplementary Treatments

Some evidence of benefit:

- **Anti-allergy:**
 - Cetirizine 10mg orally daily for 6 months may cause remission in women who fail to get complete resolution of symptoms with suppressive fluconazole ⁹⁷ (Grade 2C)

- Zafirlukast 20mg orally twice daily for 6 months may be considered as maintenance prophylaxis for recurrent VVC, particularly in women with a history of atopy ¹²⁶ (Grade 2C) (Zafirlukast production was discontinued in the UK in 2018, commercial reasons are cited for this decision and it is stressed that there were no safety concerns; the closest available alternative is Montelukast but this has not been studied in the setting of VVC).

Insufficient or no evidence of benefit:

- **Probiotics:** there continues to be insufficient evidence to support the use of oral or vaginal probiotics (mainly *Lactobacilli*) for the treatment or prevention of VVC:
 - An increasing number of studies suggest that their adjunctive use may improve clinical outcomes or reduce the likelihood of recurrence, however, the quality of evidence is variable and inconsistent in terms of the probiotic or regimen used ^{85, 127}
 - The mode of action might be via modulation of inflammatory processes rather than competition with *Candida*. ¹²⁸
- **Tea tree and other essential oils:** are antifungal in vitro but they may cause hypersensitivity reactions. ^{85, 129} There is insufficient evidence to recommend use in recurrent VVC. ⁸⁵
- **Breathable underwear with antimicrobial protection:** there is insufficient evidence to recommend their use in recurrent VVC. Small studies have shown a reduction in itching, burning, erythema and recurrences compared with cotton briefs in women with recurrent VVC on a standard fluconazole suppressive regimen. ¹³⁰
- **Yoghurt and honey mixes:** there is insufficient evidence to support the use of vaginal applications of yoghurt and honey mixes although there have been some reports of benefit with symptom improvement. ^{131, 132}
- **Diet:** there is no evidence to support any dietary modifications, including reducing carbohydrate or yeast intake. ^{95, 133}
- **Oral garlic:** there is no evidence of benefit from oral garlic on *Candida* colonisation. ¹³⁴ Observational studies have shown that garlic taken orally may cause heartburn, nausea, diarrhoea, flatulence, bloating, and an offensive body odour. ⁸⁵

Diabetes Mellitus

Recommendations:

- Known diabetic women with poor glycaemic control should be encouraged to improve this
- Fluconazole 150mg orally as a single dose for confirmed *C. albicans* in diabetic women with acute VVC (1C)
- Treat as per the recommendations above for non-*albicans Candida* in diabetic women (1C)

Symptomatic VVC is more prevalent in diabetic women and most problematic in those with poor glycaemic control. Non-*albicans Candida* species are more prevalent than in non-diabetic women, in particular *C. glabrata*.¹³⁵⁻¹³⁷

In diabetic women with symptomatic VVC where *C. albicans* is isolated single-dose fluconazole (150mg) gives a similar response to non-diabetics.¹³⁶ (Grade 1C) In diabetic women with symptomatic VVC due to *C. glabrata* treatment with boric acid 600mg suppository intravaginally at night for 14 consecutive nights achieved a higher mycological cure rate at 15 days compared to fluconazole 150mg orally as a single dose.¹³⁸ No studies have compared nystatin pessaries with boric acid in diabetic women.

HIV Infection

Recommendation:

- Treatment regimens for HIV-positive women should be the same as for HIV-negative women (1C)
- Please refer to www.hiv-druginteractions.org.uk to check for drug interaction between antifungals and antiretrovirals.

VVC occurs more frequently and with greater persistence in HIV-infected women.^{139, 140} Increased HIV shedding in the vagina, plasma HIV load above 1000 copies/mL, CD4 lymphocyte count below 200 cells/mm³ and the absence of antiretroviral therapy (ART) have been associated with an increased risk of symptomatic VVC.^{35, 140} There is no evidence to suggest that HIV-infected women respond less well to conventional methods than HIV-negative women. Treatment for HIV-infected women should be as for HIV-negative women following the recommendations above including the use of suppression therapy as necessary.¹⁴¹ (Grade 1C)

It is important to state that VVC is not a risk factor in the acquisition of HIV. ¹⁸

Hormones and Contraception

Recommendations: _

- HRT is associated with an increased risk of VVC; women on HRT with recurrent or persistent VVC should be made aware of this (1C)
- Women with recurrent VVC using COC, Cu-IUD* or LNG-IUS* may wish to trial alternative contraception but should be cautioned that the evidence supporting an association is weak and conflicting (2C)
- *The Cu-IUD and LNG-IUS are highly effective methods of contraception. If removal of either device is considered the woman should be offered suitable, effective alternative contraception. If an acceptable alternative is not available, a careful risk-benefit assessment should be made taking into consideration that keeping the Cu-IUD or LNG-IUS and controlling the recurrent VVC symptoms may be a more appropriate option for some patients.

In immunocompetent women there is a strong link between *Candida* and hormonal status. This is evidenced by *Candida* species only being found in pubertal/post pubertal and not pre-pubertal females. ¹⁴² Also postmenopausal women taking HRT are significantly more prone to develop VVC than women who are not and those with VVC are likely to have been susceptible to it before menopause. ²⁰

There is some evidence that combined oral contraceptive (COC) users may have an increased risk of VVC however there are inconsistencies with some studies finding no association, one study with a negative association and the quality of the evidence is mixed. ^{18, 143, 144} An in vitro study has shown adhesion of *Candida* to the vaginal ring surface, but a clinical study did not demonstrate a higher incidence of VVC compared to users of COC. ^{145, 146}

In theory certain progestogen-only methods (desogestrel progestogen-only pill [POP], progestogen-only implant, depot medroxyprogesterone acetate [DMPA]) should reduce the likelihood of VVC because they induce anovulation and lower oestrogen levels but there is limited evidence to support this. A systematic review looking at the progestogen-only injection identified four studies with conflicting results (two found no difference in VVC compared with controls, one found a significant decreased risk and one found a significant increased risk of VVC). ¹⁸ One observational study reported a significant lower *Candida* carriage rate in users of the progestogen-only implant and POP than users of copper intrauterine device (Cu-IUD) or

levonorgestrel intrauterine system (LNG-IUS).¹⁴⁴ A large observational study found an association between VVC and progestogen-only implant but no other methods, however only 0.4% of study participants were progestogen-only implant users so the association should be interpreted with caution.¹⁴⁷

The Cu-IUD has been identified as a possible risk factor for both acute and recurrent VVC.¹⁴⁸ There is some evidence that *Candida* can adhere to a Cu-IUD and produced a biofilm.^{149, 150} For both Cu-IUD and LNG-IUS users there is mixed evidence of limited quality with some studies suggesting higher rates of *Candida* infection whilst others show an increase in *Candida* present but no difference in symptomatic cases.^{144, 151 -}

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Reactions to Treatment

- The most common treatment-related adverse events reported in the patients who received 150 mg single dose fluconazole for VVC were headache, nausea, and abdominal pain.
- Anaphylaxis has been reported rarely with fluconazole and itraconazole
- There is a low risk of idiosyncratic drug-induced hepatitis with oral azoles; fluconazole is less frequently associated with hepatotoxicity than itraconazole
- Topical azole therapies and other topical agents can cause vulvovaginal irritation and this should be considered if symptoms worsen or persist.

FOLLOW-UP

- Follow-up and test of cure for patients with acute VVC is unnecessary if symptoms resolve.
- Patients with recurrent VVC should be advised to return if they experience poor or partial response to therapy; repeat microscopy and culture is indicated to assess for microbiological cure or new resistance
- Patients who demonstrate microbiological response but not clinical response to therapy should be reassessed for alternative causes of their symptoms
- On completion of suppressive therapy patients should be advised about the management of future acute episodes (as per acute VVC) and when to return for review (e.g. if frequency of recurrence >4 episodes per year or acute symptoms do not settle with treatment).

CONTACT TRACING & TREATMENT

There is no evidence to support the treatment of asymptomatic male sexual partners in acute or recurrent VVC.¹⁵⁵⁻¹⁵⁸ (Grade 1A)

CONSIDERATION OF RESOURCE IMPLICATIONS

- It is acknowledged that some tests, e.g. for the precise speciation of *Candida*, may not be available in all settings
- There are supply and availability issues with some non-azole treatment options, please see the relevant section above for more detail and discuss with your local pharmacist for up to date information.

QUALIFYING STATEMENT

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been taken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

AUDITABLE OUTCOMES

- Fluconazole used first line for acute VVC in non-pregnant women and women with no evidence of pregnancy risk or other contraindications to therapy. Performance Standard 90%.
- All women with recurrent VVC to be offered a genital examination performed by an appropriately trained clinician. Performance Standard 90%.
- All women with suspected recurrent VVC should have microscopy and/or culture with speciation and sensitivity testing for at least 2 (of the ≥ 4 per year) episodes (including at least one culture). Performance Standard 90%.

- Documentation of a discussion around the offer of suppressive or alternative long term therapy for all women with proven recurrent VVC. Performance Standard 90%.
- Documentation of a discussion about what constitutes good vulval skin care for all women with recurrent VVC. Performance Standard 90%.

RECOMMENDATIONS FOR FUTURE RESEARCH

- Further assessment of sensitivity and specificity of molecular and rapid antigen detection point of care diagnostic tests and the value of their use in a service providing level 3 STI care
- Appropriate regimen and duration of therapy for women that have a recurrence of symptoms after completing 6 months of treatment for recurrent VVC
- Further assessment of the benefit of treating asymptomatic colonisation with *Candida* in pregnancy on pregnancy outcome

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- treatment preferences
- ensuring the guideline covers all issues important to patients
- the language of the guideline is appropriately respectful to patients (acknowledging the intended audience is healthcare professionals).

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REFERENCES

1. Holland J, Young ML, Lee O, et al. Vulvovaginal carriage of yeasts other than *Candida albicans*. *Sex Transm Infect* 2003;79(3):249-250.
2. Wang FJ, Zhang D, Liu ZH et al. Species Distribution and *In Vitro* Antifungal Susceptibility of Vulvovaginal *Candida* Isolates in China. *Chin Med J (Engl)* 2016;129(10):1161-5.
3. Guerrero-Lozano I, Aznar-Marin P, Garcia-Agudo, L, et al. 4. Vulvovaginal candidosis by non-*albicans* *Candida* species. *Mycoses* 2012;55(Suppl4):95–338.
4. Bulik CC, Sobel JD, Nailor MD. Susceptibility profile of vaginal isolates of *Candida albicans* prior to and following fluconazole introduction - impact of two decades. *Mycoses* 2011;54(1):34-8.
5. Marchaim D, Lemanek L, Bheemreddy S, et al. Fluconazole-Resistant *Candida albicans* Vulvovaginitis. *Obstet Gynecol* 2012;120:1407–14.
6. Gross NT, Arias ML, Moraga M et al. Species Distribution and Susceptibility to Azoles of Vaginal Yeasts Isolated Prostitutes. *Infect Dis Obstet Gynecol* 2007:82412.
7. Araj GF, Asmar RG, Avedissian AZ. *Candida* profiles and antifungal resistance evolution over a decade in Lebanon. *J Infect Dev Ctries* 2015;9(9):997-1003.
8. Hetticarachchi N, Ashbee HR, Wilson JD. Prevalence and management of non-*albicans* vaginal candidiasis. *Sex Transm Infect* 2010;86(20):99-100.
9. Dennerstein GJ, Ellis DH, Reed CS et al. Pathogenicity of non-*albicans* yeasts in the vagina. *J Low Genit Tract Dis* 2011;15(1):33-6.
10. Zeng J, Zong LL, Mao T, et al. Distribution of *Candida albicans* genotype and *Candida* species is associated with the severity of vulvovaginal candidiasis. *Nan Fang Yi Ke Da Xue Xue Bao* 2011;31(10):1649-53.
11. Hurley R, De Louvois J. *Candida* vaginitis. *Postgrad Med J* 1979;55:645–47.
12. Denning DW, Kneale M, Sobel JD, et al. Global burden of recurrent vulvovaginal candidiasis: a systematic review. *Lancet Inf Dis* 2018 Nov;18:e339-e347.
13. Hurley R. Recurrent *Candida* infection. *Clin Obstet Gynaecol* 1981;8(1):209-14.
14. Foxman B, Muraglia R, Dietz JP, et al. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: Results from an internet panel survey. *J Low Genit Tract Dis* 2013;17(3):340-5.

15. Fidel PL, Jr., Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. *Clin Microbiol Rev* 1996;9(3):335-48.
16. El-Din SS, Reynolds MT, Ashbee HR, Barton RC, Evans EG. An investigation into the pathogenesis of vulvovaginal candidosis. *Sex Transm Infect* 2001;77(3):179-183.
17. Patel D, Gillespie B, Sobel J, et al. Risk factors for recurrent vulvovaginal candidiasis in women receiving maintenance antifungal therapy: results of a prospective cohort study. *Am J Obstet Gynecol* 2004;190(3):644-653.
18. van de Wijgert JH, Verwijs MC, Turner AN, et al. Hormonal contraception decreases bacterial vaginosis but oral contraception may increase candidiasis: implications for HIV transmission. *AIDS* 2013;27(13):2141-53.
19. Donders GG, Mertens I, Bellen G, et al. Self-elimination of risk factors for recurrent vaginal candidosis. *Mycoses* 2011;54(1):39-45.
20. Fischer G, Bradford J. Vulvovaginal candidiasis in postmenopausal women: the role of hormone replacement therapy. *J Low Genit Tract Dis* 2011;15(4):263-7.
21. Pirotta MV, Garland SM. Genital Candida species detected in samples from women in Melbourne, Australia, before and after treatment with antibiotics. *J Clin Microbiol* 2006;44(9):3213-7.
22. Oliveira CS, Gandra R, Loth EA, et al. Clinical, Epidemiological and laboratory findings among women with recurrent vulvovaginal candidiasis (RVVC) in an university hospital, Brazil. *Mycoses* 2015;58(Suppl3):68(P038).
23. Yano J, Kolls JK, Happel KI, et al. The Acute Neutrophil Response Mediated by S100 Alarmins during Vaginal Candida Infections Is Independent of the Th17-Pathway. *PLoS ONE* 2012; 7(9): e46311.
24. Odds FC, Webster CE, Mayuranathan P, et al. Candida concentrations in the vagina and their association with signs and symptoms of vaginal candidosis. *J Med Vet Mycol* 1988;26(5):277-83.
25. Fidel PL, Barousse M, Espinosa T, et al. An Intravaginal Live Candida Challenge in Humans Leads to New Hypotheses for the Immunopathogenesis of Vulvovaginal Candidiasis. *Infect Immun* 2004; 72(5): 2939–2946.
26. Moraes PS. Recurrent vaginal candidiasis and allergic rhinitis: a common association. *Ann Allergy Asthma Immunol* 1998;81(2):165-9.
27. Ehrstrom S, Kornfeld D, Rylander E. Perceived stress in women with recurrent vulvovaginal candidiasis. *J Psychosom Obstet Gynaecol* 2007;28(3):169-76.
28. Akimoto-Gunther L, Bonfim-Mendonça PdS, Takahachi G, et al. Highlights Regarding Host Predisposing Factors to Recurrent Vulvovaginal Candidiasis: Chronic Stress and Reduced Antioxidant Capacity. *PLoS ONE* 2016 11(7): e0158870.

29. Spacek J, Jilek P, Buchta V, et al. The serum levels of calcium, magnesium, iron and zinc in patients with recurrent vulvovaginal candidosis during attack, remission and in healthy controls. *Mycoses* 2005;48(6):391-395.
30. Naderi N, Etaati Z, Rezvani Joibari M, et al. Immune deviation in recurrent vulvovaginal candidiasis: Correlation with Iron Deficiency Anemia. *Iran J Immunol* 2013;10(2):118-26
31. Bohler K, Meisinger V, Klade H, et al. Zinc levels of serum and cervicovaginal secretion in recurrent vulvovaginal candidiasis. *Genitourin-Med* 1994;70(5):308-310.
32. Henić E, Thiel S, Mårdh PA. Mannan-binding lectin in women with a history of recurrent vulvovaginal candidiasis. *Eur J Obstet Gynecol Reprod Biol* 2010;148(2):163-5.
33. Donders GG, Babula O, Bellen G, et al. Mannose-binding lectin gene polymorphism and resistance to therapy in women with recurrent vulvovaginal candidiasis. *BJOG* 2008;115(10):1225-31.
34. Nedovic B, Posteraro B, Leoncini E, et al. Mannose-binding lectin codon 54 gene polymorphism and vulvovaginal candidiasis: a systematic review and meta-analysis. *Biomed Res Int* 2014;738298-99.
35. Apalata T, Longo-Mbenza B, Sturm A, et al. Factors Associated with Symptomatic Vulvovaginal Candidiasis: A Study among Women Attending a Primary Healthcare Clinic in Kwazulu-Natal, South Africa. *Ann Med Health Sci Res* 2014;4(3):410-6.
36. Narayankhedkar A, Hodiwala A, Mane A. Clinicoetiological Characterization of Infectious Vaginitis amongst Women of Reproductive Age Group from Navi Mumbai, India. *J Sex Transm Dis* 2015;817092.
37. Beikert FC, Le MT, Koeninger A, et al. Recurrent vulvovaginal candidosis: focus on the vulva. *Mycoses* 2011;54(6):e807-10.
38. Zhu YX, Li T, Fan SR, et al. Health-related quality of life as measured with the Short-Form 36 (SF-36) questionnaire in patients with recurrent vulvovaginal candidiasis. *Health Qual Life Outcomes* 2016;14:65.
39. Hong E, Dixit S, Fidel PL, et al. Vulvovaginal candidiasis as a chronic disease: diagnostic criteria and definition. *J Low Genit Tract Dis* 2014;18(1):31-8.
40. Spacek J, Buchta V, Jílek P, et al. Clinical aspects and luteal phase assessment in patients with recurrent vulvovaginal candidiasis. *Eur J Obstet Gynecol Reprod Biol* 2007;131(2):198-202.
41. Schaaf VM, Perez-Stable EJ, Borchardt K. The limited value of symptoms and signs in the diagnosis of vaginal infections. *Arch Intern Med* 1990;150(9):1929-1933.
42. Geiger AM, Foxman B, Sobel JD. Chronic vulvovaginal candidiasis: characteristics of women with *Candida albicans*, *C glabrata* and no candida. *Genitourin-Med* 1995;71(5):304-307.
43. Lanternier F, Cypowyj S, Picard C, et al. Primary immunodeficiencies underlying fungal infections. *Curr Opin Pediatr* 2013;25(6):736-47.
44. Ferris DG, Dekle C, Litaker MS. Women's use of over-the-counter antifungal medications for gynaecologic symptoms. *J Fam Pract* 1996;42(6):595-600.
45. Lev-Sagie A, Witkin SS. Recent advances in understanding provoked vestibulodynia. *F1000Res* 2016;5:2581.

46. Harlow BL, Caron RE, Parker SE, et al. Recurrent Yeast Infections and Vulvodynia: Can We Believe Associations Based on Self-Reported Data? *J Womens Health (Larchmt)* 2017;26(10):1069-1076.
47. Mason MJ, Winter AJ. How to diagnose and treat aerobic and desquamative inflammatory vaginitis. *Sex Transm Infect* 2017;**93**:8-10.
48. Cibley LJ, Cibley LJ. Cytolytic vaginosis. *Am J Obstet Gynecol* 1991;165(4 Pt 2):1245-9.
49. Xu H, Zhang X, Yao W, et al. Characterization of the vaginal microbiome during cytolytic vaginosis using high-throughput sequencing. *J Clin Lab Anal* 2018;10:e22653
50. Lindner JG, Plantema FH, Hoogkamp K. Quantitative studies of the vaginal flora of healthy women and of obstetric and gynaecological patients. *J Med Microbiol* 1978; 11(3):233-24.
51. Odds FC. *Candida and Candidosis; A review and bibliography*. Second ed. London: Bailliere Tindall; 1988.
52. Abbott J. Clinical and microscopic diagnosis of vaginal yeast infection: a prospective analysis. *Ann Emerg Med* 1995; 25(5):587-591.
53. Bergman JJ, Berg AO, Schneeweiss R, et al. Clinical comparison of microscopic and culture techniques in the diagnosis of *Candida* vaginitis. *J Fam Pract* 1984; 18(4):549-552.
54. Eckert LO, Hawes SE, Stevens CE, et al. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. *Obstet Gynecol* 1998; 92(5):757-765.
55. Sonnex C, Lefort W. Microscopic features of vaginal candidiasis and their relation to symptomatology. *Sex Transm Infect* 1999; 75(6):417-419.
56. Zdolsek B, Hellberg D, Froman G, et al. Culture and wet smear microscopy in the diagnosis of low-symptomatic vulvovaginal candidosis. *Eur J Obstet Gynecol Reprod Biol* 1995;58(1):47-51.
57. Liu XP, Fan SR. Methylrosaniline chloride stained vaginal smears for the diagnosis of vulvovaginal candidiasis. *Int J Gynaecol Obstet* 2007;99(2):83-6.
58. Hopwood V, Crowley T, Horrocks CT, et al. Vaginal candidosis: relation between yeast counts and symptoms and clinical signs in non-pregnant women. *Genitourin-Med* 1988;64(5):331-334.
59. Odds FC, Webster CE, Riley VC, et al. Epidemiology of vaginal *Candida* infection: significance of numbers of vaginal yeasts and their biotypes. *Eur J Obstet Gynecol Reprod Biol* 1987;25(1):53-66.
60. Odds FC, Webster CE, Mayuranathan P, et al. *Candida* concentrations in the vagina and their association with signs and symptoms of vaginal candidosis. *J Med Vet Mycol* 1988; 26(5):277-283.
61. Priestley CJ, Jones BM, Dhar J, Goodwin L. What is normal vaginal flora? *Genitourin-Med* 1997;73(1):23-28.
62. Singh RH, Erbeling EJ, Zenilman JM, et al. The role of the speculum and bimanual examinations when evaluating attendees at a sexually transmitted diseases clinic. *Sex Transm Infect* 2007 83:206-1.
63. Barnes P, Vieira R, Chauhan M. Self-taken vaginal swabs versus clinician-taken for detection of *Candida* and bacterial vaginosis: a case-control study in primary care. *Br J Gen Pract* 2017;67(665):e824-e829.
64. Royal College of General Practitioners (RCGP)/ British Association for Sexual Health and HIV (BASHH). Sexually Transmitted Infections in Primary Care. 2013 Available at:

<https://www.bashhguidelines.org/media/1089/sexually-transmitted-infections-in-primary-care-2013.pdf> (accessed: 29/01/2019)

65. Standards Unit, Microbiology Services, Public Health England. UK Standards for Microbiology Investigations: Investigations of Genital Tract and Associated Specimens. 2017 B28i4.6. <https://www.gov.uk/government/publications/smi-b-28-investigation-of-genital-tract-and-associated-specimens> (Date Accessed: 27/03/2019)
66. Engberts MK, Boon ME, van Haaften M, et al. Symptomatic candidiasis: Using self sampled vaginal smears to establish the presence of *Candida*, *Lactobacilli*, and *Gardnerella vaginalis*. *Diagn Cytopathol* 2007;35(10):635-9.
67. Vergers-Spooren HC1, van der Meijden WI, Luijendijk A, et al. Self-sampling in the diagnosis of recurrent vulvovaginal candidosis. *J Low Genit Tract Dis* 2013;17(2):187-92.
68. Danby CS, Boikov D, Rautemaa-Richardson R, et al. Effect of pH on in vitro susceptibility of *Candida glabrata* and *Candida albicans* to 11 antifungal agents and implications for clinical use. *Antimicrob Agents Chemother* 2012;56(3):1403-6.
69. Spitzer M, Wiederhold NP. Reduced Antifungal Susceptibility of Vulvovaginal *Candida* Species at Normal Vaginal pH Levels: Clinical Implications. *J Low Genit Tract Dis* 2018;22(2):152-158
70. Cartwright CP, Lembke BD, Ramachandran K, et al. Comparison of nucleic acid amplification assays with BD affirm VPIII for diagnosis of vaginitis in symptomatic women. *J Clin Microbiol* 2013;51(11):3694-9.
71. Chatwani AJ, Mehta R, Hassan S, et al. Rapid testing for vaginal yeast detection: a prospective study. *Am J Obstet Gynecol* 2007;196(4):309.
72. Dan M, Leshem Y, Yeshaya A, et al. Performance of a rapid yeast test in detecting *Candida* spp. in the vagina. *Diagn Microbiol Infect Dis* 2010;67(1):52-5.
73. Elegbe IA, Elegbe I. Quantitative relationships of *Candida albicans* infections and dressing patterns in Nigerian women. *Am J Public Health* 1983;73(4):450-452.
74. Ekpenyong CE, Inyang-etoh EC, Ettebong EO, et al. Recurrent vulvovaginal candidosis among young women in south eastern Nigeria: The role of lifestyle and health-care practices. *Int J STD AIDS* 2012;23(10):704-9.
75. Pontes AC, Amaral RL, Giraldo PC, et al. A systematic review of the effect of daily panty liner use on the vulvovaginal environment. *Int J Gynaecol Obstet* 2014;127(1):1-5.
76. Giraldo PC, Amaral RL, Juliato C, et al. The effect of "breathable" panty liners on the female lower genital tract. *Int J Gynaecol Obstet* 2011;115(1):61-4
77. Janković S, Bojović D, Vukadinović D, et al. Risk factors for recurrent vulvovaginal candidiasis. *Vojnosanit Pregl* 2010;67(10):819-24.
78. Shaaban OM, Abbas AM, Moharram AM, et al. Does vaginal douching affect the type of candidal vulvovaginal infection? *Med Mycol* 2015;53(8):817-27.

79. Heng LS, Yatsuya H, Morita S, et al. Vaginal douching in Cambodian women: its prevalence and association with vaginal candidiasis. *J Epidemiol* 2010;20(1):70-6.
80. Edwards L, Lynch P. Genital Dermatology Atlas. 2nd Ed. Philadelphia: Lippincott Williams and Wilkins, 2004.
81. Watson C, Fairley C, Garland S, et al. The effect of sexual intercourse on vaginal colonisation with candida. *Sex Transm Infect* 2015;91:A119-A120 (P06.14).
82. Eisen DP, Minchinton RM. Impact of Mannose-Binding Lectin on Susceptibility to Infectious Diseases. *CID* 2003;37:1496-1505.
83. Watson MC, Grimshaw JM, Bond CM, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush): a systematic review. *Int J Gynaecol Obstet* 2002; 109(1):85-95.
84. Nurbhai M, Grimshaw J, Watson M, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database Syst Rev* 2007;4: CD002845.
85. Lopez M, Ester J. Candidiasis (vulvovaginal). *BMJ Clin Evid* 2015:0815.
86. Pitsouni E, Iavazzo C, Falagas ME. Itraconazole vs fluconazole for the treatment of uncomplicated acute vaginal and vulvovaginal candidiasis in nonpregnant women: a metaanalysis of randomized controlled trials. *Am J Obstet Gynecol* 2008;198(2):153-60.
87. Sekhavat L, Tabatabaie A, Tezerjani FZ. Oral fluconazole 150 mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. *J Infect Public Health* 2011;4(4):195-9.
88. Mølgaard-Nielsen D, Svanström H, Melbye M, et al. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. *JAMA* 2016;315(1):58-67.
89. Daniel S, Rotem R, Koren G, et al. Vaginal antimycotics and the risk for spontaneous abortions. *Am J Obstet Gynecol* 2018;218(6):601.e1-601.e7
90. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines 2015. (<http://www.cdc.gov/std/tg2015/default.htm>)
91. Sobel JD, Kapernick PS, Zervos M, et al. Treatment of complicated Candida vaginitis: comparison of single and sequential doses of fluconazole. *Am J Obstet Gynecol* 2001;185(2):363-369.
92. Sobel JD, Brooker D, Stein GE, et al. Single oral dose fluconazole compared with conventional clotrimazole topical therapy of Candida vaginitis. Fluconazole Vaginitis Study Group. *Am J Obstet Gynecol* 1995;72(4 Pt 1):1263-1268.
93. Fan S, Liu X, Liang Y. Miconazole nitrate vaginal suppository 1,200 mg versus oral fluconazole 150 mg in treating severe vulvovaginal candidiasis. *Gynecol Obstet Invest* 2015;80(2):113-8.
94. Zhou X, Li T, Fan S, et al. The efficacy and safety of clotrimazole vaginal tablet vs. oral fluconazole in treating severe vulvovaginal candidiasis. *Mycoses* 2016;59(7):419-28.

95. Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *Am J Obstet Gynecol* 1998;178(2):203-211.
96. Rosa MI, Silva BR, Pires PS, et al. Weekly fluconazole therapy for recurrent vulvovaginal candidiasis: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2013;167(2):132-6.
97. Neves NA, Carvalho LP, Lopes AC, et al. Successful treatment of refractory recurrent vaginal candidiasis with cetirizine plus fluconazole. *J Low Genit Tract Dis* 2005;9(3):167-70.
98. Perlin DS, Shor E, Zhao Y. Update on antifungal drug resistance. *Curr Clin Microbiol Rep*. 2015;2:84–95
99. European Medicines Agency. Press release 26/07/2013:
<https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-suspension-marketing-authorisations-oral-ketoconazole> (date accessed 04/02/2019)
100. Donders G, Bellen G, Byttebier G, et al. Individualized decreasing-dose maintenance fluconazole regimen for recurrent vulvovaginal candidiasis (ReCiDiF trial). *Am J Obstet Gynecol* 2008;199(6):613.
101. Nguyen Y, Lee A, Fischer G. Management of chronic vulvovaginal candidiasis: A long term retrospective study. *Australas J Dermatol* 2017;58(4):e188-e192
102. Sobel J, Chaim W, Nagappan V, et al. Treatment of vaginitis caused by *Candida glabrata*: use of topical boric acid and flucytosine. *Am J Obstet Gynecol* 2003;189(5):1297-1300.
103. Singh S, Sobel J, Bhargava P, et al. Vaginitis due to *Candida krusei*: epidemiology, clinical aspects, and therapy. *Clin Infect Dis* 2002;35(9):1066-70.
104. Dressen G, Kusche W, Neumeister C, et al. Diagnosis of vulvovaginal Candidiasis and effectiveness of combined topical treatment with nystatin: Results of a non-interventional study in 973 patients. *Open Womens Health J* 2012;6:19-23.
105. Khameneie KM, Arianpour N, Roozegar R, et al. Fluconazole and Boric Acid for Treatment of Vaginal Candidiasis--New Words About Old Issue. *East Afr Med J* 2013;90(4):117-23.
106. Iavazzo C, Gkegkes ID, Zarkada IM, et al. Boric Acid for Recurrent Vulvovaginal Candidiasis: The Clinical Evidence. *J Womens Health (Larchmt)* 2011;20(8):1245-55.
107. Guaschino S, De Seta F, Sartore A, et al. Efficacy of maintenance therapy with topical boric acid in comparison with oral itraconazole in the treatment of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 2001;184(4):598-602.
108. Acs N, Bunhidy F, Puh E, et al. Teratogenic effects of vaginal boric acid treatment during pregnancy. *Int J Gynaecol Obstet* 2006;93(1):55-6.
109. Phillips A. Treatment of non-albicans *Candida* vaginitis with amphotericin B vaginal suppositories. *Am J Obstet Gynecol* 2005;192(6):2009-2012.
110. White DJ, Habib AR, Vanthuyne A, et al. Combined topical flucytosine and amphotericin B for refractory vaginal *Candida glabrata* infections. *Sex Transm Infect* 2001;77(3):212-213.
111. Fan S, Liu X, Wu C, et al. Vaginal nystatin versus oral fluconazole for the treatment for recurrent vulvovaginal candidiasis. *Mycopathologia* 2015;179(1-2):95-101.

112. Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy. *Cochrane Database Syst Rev*. 2001;(4):CD000225.
113. Bauters T, Dhont M, Temmerman M, I, Nelis H. Prevalence of vulvovaginal candidiasis and susceptibility to fluconazole in women. *Am J Obstet Gynecol* 2002;187(3):569-574.
114. Kent Pharmaceuticals Ltd. Fluconazole 150mg Capsules: Summary of Product Characteristics. <https://www.medicines.org.uk/emc/product/3246/smpc> (date accessed: 31/07/2019)
115. Alsaad AM, Kaplan YC, Koren G. Exposure to fluconazole and risk of congenital malformations in the offspring: A systematic review and meta-analysis. *Reprod Toxicol* 2015;52:78-82.
116. Howley MM, Carter TC, Browne ML, et al. Fluconazole use and birth defects in the National Birth Defects Prevention Study. *Am J Obstet Gynecol* 2016;214(5):657.
117. Mogensen DM, Pihl MB, Skakkebaek NE, et al. Prenatal exposure to antifungal medication may change anogenital distance in male offspring: a preliminary study. *Environ Health* 2017;16(1):68.
118. National Poisons Information Service. www.toxbase.org (date accessed 11/04/2019)
119. Cotch MF, Hillier SL, Gibbs RS, Eschenbach DA. Epidemiology and outcomes associated with moderate to heavy Candida colonisation during pregnancy. Vaginal Infections and Prematurity Study Group. *American Journal of Obstetrics & Gynecology* 1998; 178(2):374-380.
120. Farr A, Kiss H, Holzer I, et al. Effect of asymptomatic vaginal colonisation with *Candida albicans* on pregnancy outcome. *Acta Obstet Gynecol Scand* 2015;94(9):989-96.
121. Bánhidý F, Dudás I, Czeizé AE. Preconceptional screening of sexually transmitted infections/diseases. *Cent Eur J Med* 2010;6(1):49-57.
122. Roberts CL, Algert CS, Rickard KL, et al. Treatment of vaginal candidiasis for the prevention of preterm birth: a systematic review and meta-analysis. *Syst Rev* 2015;21;4:31.
123. Tellapragada C, Eshwara VK, Bhat P, et al. Screening of vulvovaginal infections during pregnancy in resource constrained settings: Implications on preterm delivery. *J Infect Public Health* 2017;10(4):431-437.
124. Lewis H, Pruski P, Kindinger L, et al. Relationship Between Yeast, Vaginal Microbiota Composition and Pregnancy Outcomes. *Reprod Sci* 2017;24;s1:1A-51A
125. Holzer I, Farr A, Kiss H, et al. The colonisation with *Candida* species is more harmful in the second trimester of pregnancy. *Arch Gynecol Obstet* 2017;295(4):891-895.
126. White DJ, Vanthuyne A, Wood PM, et al. Zafirlukast for severe recurrent vulvovaginal candidiasis: an open label pilot study. *Sex Transm infect* 2004;80(3).
127. Xie HY, Feng D, Wei DM, et al. Probiotics for vulvovaginal candidiasis in non-pregnant women. *Cochrane Database Syst Rev* 2017;11:CD010496.
128. Kalliomaki M, Salminen S, Arvilommi H, et al. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357(9262):1076-1079.

129. Hammer KA, Carson CF, Riley TV. In-vitro activity of essential oils, in particular *Melaleuca alternifolia* (tea tree) oil and tea tree oil products, against *Candida* spp. *J Antimicrob Chemother* 1998;42(5):591-595.
130. D'Antuono A, Baldi E, Bellavista S, et al. Use of Dermal silk briefs in recurrent vulvovaginal candidosis: safety and effectiveness. *Mycoses* 2012;55(3):e85-9.
131. Abdelmonem AM, Rasheed SM, Mohamed AS. Bee-honey and yogurt: a novel mixture for treating patients with vulvovaginal candidiasis during pregnancy. *Arch Gynecol Obstet* 2012;286(1):109-14.
132. Darvishi M, Jahdi F, Hamzegardeshi Z, et al. The Comparison of vaginal cream of mixing yogurt, honey and clotrimazole on symptoms of vaginal candidiasis. *Glob J Health Sci* 2015;7(6):108-16.
133. Mardh PA, Rodrigues AG, Genc M, et al. Facts and myths on recurrent vulvovaginal candidosis--a review on epidemiology, clinical manifestations, diagnosis, pathogenesis and therapy. *Int J STD AIDS* 2002; 3(8):522-539.
134. Watson CJ, Grando D, Fairley CK, et al. The effects of oral garlic on vaginal candida colony counts: a randomised placebo controlled double-blind trial. *BJOG* 2014;121(4):498-506.
135. Bohannon NJ. Treatment of vulvovaginal candidiasis in patients with diabetes. *Diabetes care* 1998;21(3):451-456.
136. Goswami D, Goswami R, Banerjee U, et al. Pattern of *Candida* species isolated from patients with diabetes mellitus and vulvovaginal candidiasis and their response to single dose oral fluconazole therapy. *J infect* 2006;52(2):111-7.
137. Akimoto-Gunther L, Bonfim-Mendonca PS, Godoy JSR, et al. Hyperglycemia and increased risk of vulvovaginal candidiasis (VVC). *Mycoses* 2015;58(4):168 (P316).
138. Ray D, Goswami R, Banerjee U, et al. Prevalence of *Candida glabrata* and Its Response to Boric Acid Vaginal Suppositories in Comparison With Oral Fluconazole in Patients With Diabetes and Vulvovaginal Candidiasis. *Diabetes care* 2007;30(2).
139. Duerr A, Heilig CM, Meikle SF, et al. Incident and persistent vulvovaginal candidiasis among human immunodeficiency virus-infected women: Risk factors and severity. *Obstet Gynecol* 2003;101(3).
140. Apalata T, Carr WH, Sturm WA, et al. Determinants of symptomatic vulvovaginal candidiasis among human immunodeficiency virus type 1 infected women in rural KwaZulu-Natal, South Africa. *Infect Dis Obstet Gynecol* 2014;387070.
141. Sobel J. Vulvovaginal candidiasis: a comparison of HIV-positive and -negative women. *Int J STD AIDS* 2002;13(6):358-362.
142. Baka S, Tsouma I, Logothetis E, et al. Pathogens implicated in cases of vulvovaginitis in prepubertal and pubertal girls. *Clin Microbiol Infect* 2012;18:233-234(P1009).
143. Spinillo A, Pizzoli G, Colonna L, et al. Epidemiologic characteristics of women with idiopathic recurrent vulvovaginal candidiasis. *Obstet Gynecol* 1993; 81(5)(Pt 1):721-727.

144. Donders G, Bellen G, Janssens D, et al. Influence of contraceptive choice on vaginal bacterial and fungal microflora. *Eur J Clin Microbiol Infect Dis* 2017;36(1):43-48
145. Camacho DP, Consolaro ME, Patussi EV, et al. Vaginal yeast adherence to the combined contraceptive vaginal ring (CCVR). *Contraception* 2007;76(6):439-43.
146. Veres S, Miller L, Burington B. A comparison between the vaginal ring and oral contraceptive. *Obstet Gynecol* 2004;104(3):555-63.
147. Wang LY, OuYang L, Tong F, et al. The effect of contraceptive methods on reproductive tract infections risk: a cross-sectional study having a sample of 52,481 women. *Arch Gynecol Obstet* 2016;294(6):1249-1256
148. Guzel AB, Ilkit M, Akar T, et al. Evaluation of risk factors in patients with vulvovaginal candidiasis and the value of chromID Candida agar versus CHROMagar Candida for recovery and presumptive identification of vaginal yeast species. *Med Mycol* 2011; 49: 16–25.
149. Auler ME, Morreira D, Rodrigues FF, et al. Biofilm formation on intrauterine devices in patients with recurrent vulvovaginal candidiasis. *Med Mycol* 2010; **48**: 211–216.
150. Chassot F, Negri M, Svidzinski A, et al. Can intrauterine contraceptive devices be a Candida albicans reservoir. *Contraception* 2008; **77**: 359.
151. Güdücü N, Gönenç G, Işçi H, et al. Clinical importance of detection of bacterial vaginosis, trichomonas vaginalis, candida albicans and actinomyces in Papanicolaou smears. *Clin Exp Obstet Gynecol* 2012;39(3):333-6.
152. Behboudi-Gandevani S, Imani S, Moghaddam-Banaem L, et al. Can intrauterine contraceptive devices lead to VulvoVaginal Candidiasis (VVC) and Anemia in Iranian new users? *Sex Reprod Healthc* 2015;6(1):40-3.
153. Donders G, Bellen G, Ruban K, et al. Short- and long-term influence of the levonorgestrel-releasing intrauterine system (Mirena) on vaginal microbiota and Candida. *J Med Microbiol* 2018;67(3):308-313.
154. Cakiroglu Y, Caliskan S, Doger E, et al. Does removal of CU-IUD in patients with biofilm forming candida really maintain regression of clinical symptoms? *J Obstet Gynaecol* 2015;35;6:600-603
155. Bisschop MP, Merkus JM, Scheygrond H, et al. Co-treatment of the male partner in vaginal candidosis: a double-blind randomized control study. *BJOG* 1986;93(1):79-81.
156. Fong IW. The value of treating the sexual partners of women with recurrent vaginal candidiasis with ketoconazole. *Genitourin-Med* 1992;68(3):174-176.
157. Lisboa C, Costa AR, Ricardo E, et al. Genital candidosis in heterosexual couples. *J Eur Acad Dermatol Venereol* 2011;25(2):145-51.
158. Spence, D. Candidiasis (Vulvovaginal). *BMJ Clin Evid* 2010 5;2010.

EDITORIAL INDEPENDENCE

This guideline was commissioned, edited and endorsed by the BASHH CEG.

CONFLICTS OF INTEREST

All members of the guideline writing committee completed the BASHH conflict of interest declaration at the time the guideline's final draft was submitted to the CEG.

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Table 1. Clinical Features of Vulvovaginal Candidiasis and Common Differential Diagnoses – Symptoms*

	Vulvovaginal Candidiasis	Lichen Sclerosus	Vulvo- / vestibulodynia	Contact Dermatitis/Eczema	Chronic Lichen Simplex/Chronic Eczema
Vulval Itch	Yes	Yes, severe	No	Yes	Yes
Vulval soreness	Yes – but not always; ‘prickling’	Yes, severe	Burning is predominant symptom	Yes	Possible
Discharge	Yes - odourless, typically ‘curdy’ but may be thin or absent (absence does not exclude diagnosis)	No ⁺	No ⁺	Possible, but this is exudate from inflamed skin, not a true discharge	No ⁺
Superficial Dyspareunia	Possible	Yes (especially if loss of vulval architecture)	Yes – point penetration pain	Possible	Possible
Superficial dysuria	Possible	Possible	Not usually	Possible	Not usually
Swelling	Possible	No	No	Possible	Possible (secondary to lichenification – thickening of skin from chronic scratching)
Response to topical steroid	Improvement/no change/worse	Improvement but requires high potency	No	Improvement	Improvement

* the symptoms and signs listed in this table are not pathognomic of the conditions but an indication of a ‘typical clinical presentation’ and to highlight the potential differences and similarities between each of these conditions, further information about the alternative conditions listed can be found at www.bad.org.uk

⁺ unless dual pathology

Table 2. Clinical Features of Vulvovaginal Candidiasis and Common Differential Diagnoses – Signs*

	VV Candidiasis	Lichen Sclerosus	Vulvodinia	Contact Dermatitis	Chronic Lichen Simplex
Erythema	Yes	Yes but usually in conjunction with other features	Possible	Yes	Possible
Fissuring	Possible	Possible	No	Possible	Possible
Discharge	Yes - odourless, typically 'curdy' but may be thin or absent (absence does not exclude diagnosis)	No ⁺	No ⁺	Possible, but this is exudate from inflamed skin, not a true discharge	No ⁺
Oedema	Possible	No	No	Possible	Possible
Other features	Satellite lesions	Pallor, atrophy, loss of vulval architecture, areas of haemorrhage, introital narrowing	Cotton tip provoked tenderness	Erythema, exudate	Lichenification, (thickening of affected skin caused by long term scratching)
Excoriations (scratch marks)	Possible	Possible	No	Often	Often

* the symptoms and signs listed in this table are not pathognomic of the conditions but an indication of a 'typical clinical presentation' and to highlight the potential differences and similarities between each of these conditions, further information about the alternative conditions listed can be found at www.bad.org.uk

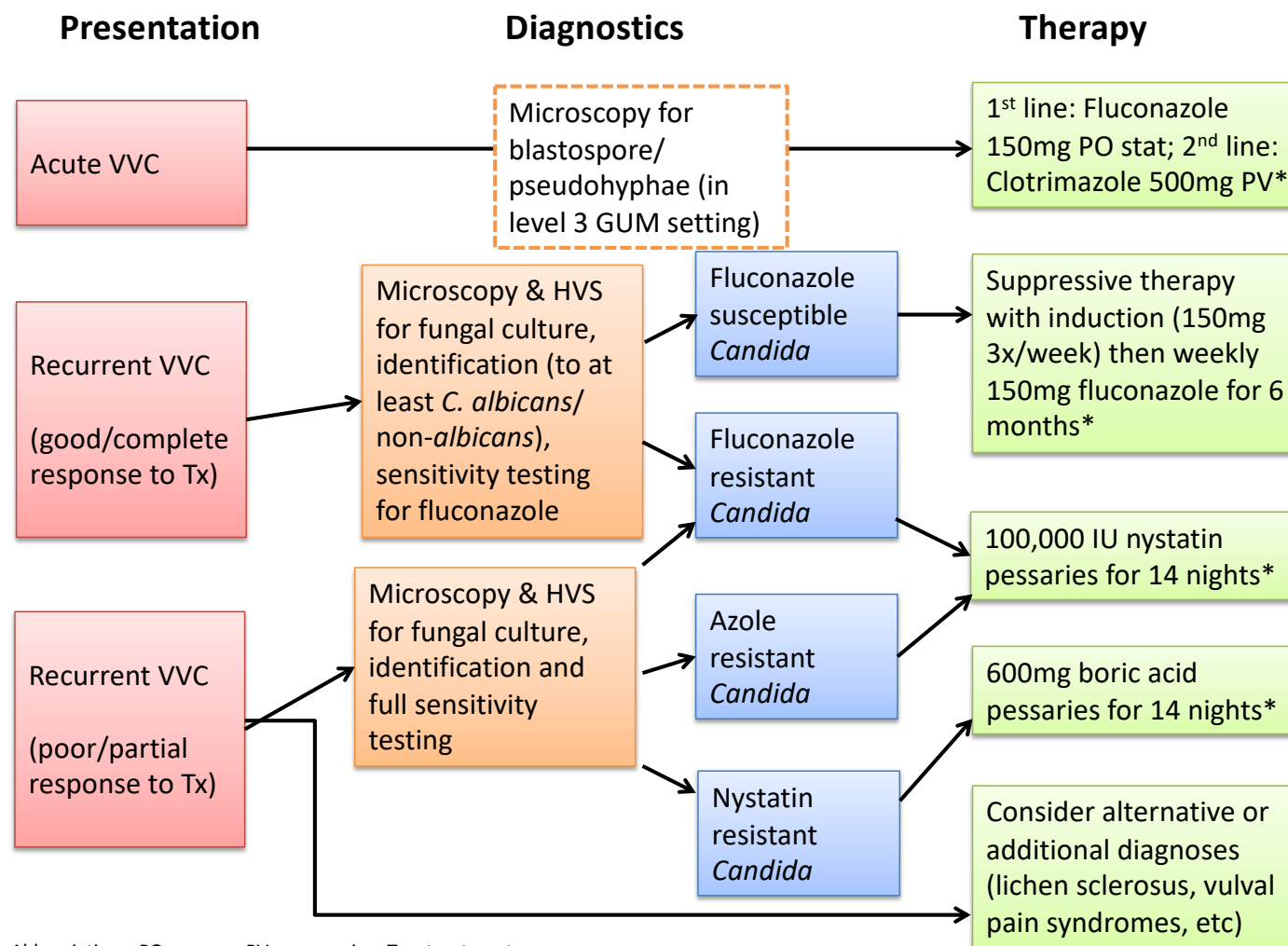
⁺ unless dual pathology

Table 3. Vulvovaginal candidiasis treatment options

		Preferred	Alternative
Acute VVC	Non-pregnant women	Fluconazole 150mg PO stat (1B) <i>If oral therapy is contraindicated:</i> Clotrimazole 500mg PV stat (1B)	Clotrimazole vaginal cream (10%) 5g stat** (1B) Clotrimazole pessary 200mg PV nocte for 3 nights** (1C) Econazole pessary 150mg PV stat or 150mg PV nocte for 3 nights** (1B) Fenticonazole capsule 600mg PV stat or 200mg PV nocte for 3 nights** (1B) Itraconazole 200mg bd for 1 day PO* (1B) Miconazole pessary 1200mg PV stat or 400mg PV nocte for 3 nights** (1B) Miconazole vaginal cream (2%) 5g PV nocte for 7 nights** (1B)
	Pregnancy	Clotrimazole pessary 500mg PV nocte for up to 7 nights (1C)	Clotrimazole vaginal cream (10%) 5g nocte for up to 7 nights** (1C) Clotrimazole pessary 200mg or 100mg PV nocte for 7 nights** (1C) Econazole pessary 150mg PV nocte for 7 nights** (1C) Miconazole pessary 1200mg or 400mg PV nocte for 7 nights** (1C) Miconazole vaginal cream (2%) 5g PV nocte for 7 nights** (1C)
	NAC sp & azole resistance	Nystatin pessaries 100,000units PV nocte for 14 days (1B)	Boric acid suppositories 600mg PV nocte for 14 nights* (1B) Amphotericin B vaginal suppositories 50mg PV nocte for 14 nights (2C) Flucytosine 5g cream or 1g pessary with amphotericin or nystatin PV nocte for 14 nights (2C)
Recurrent VVC	Non-pregnant women	Induction: fluconazole 150mg PO every 72 hours x 3 doses* (1A) Maintenance: fluconazole 150mg PO once a week for 6 months* (1A)	Induction: topical imidazole therapy can be increased to 10-14 days according to symptomatic response (2C) Maintenance for 6 months: Clotrimazole pessary 500mg PV nocte once a week (1B) or Itraconazole 50-100mg daily*(2C)
	Pregnancy	Induction: topical imidazole therapy can be increased to 10-14 days according to symptomatic response (2C) Maintenance: Clotrimazole pessary 500mg PV weekly (1C)	
	NAC sp & azole resistance	Nystatin pessaries 100,000units PV nocte for 14 nights/month for 6 months (2C)	Consider 14 nights per month for 6 month of the alternative regimens (2D)
Severe VVC		Fluconazole 150mg on day 1 and 4 (1B)	Clotrimazole pessary 500mg PV on day 1 and 4 (1B) Miconazole nitrate capsule 1200mg PV on day 1 and 4 (1B)
Breastfeeding	Topical imidazoles only should be as per the recommendations listed above for non-pregnant women with acute, recurrent VVC.		

NAC – Non-albicans *Candida*; * Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding (1B); **Creams and pessaries may damage diaphragms and latex condoms.

Figure 1. Summary of the Vulvovaginal Candidiasis diagnostic and management pathway



Abbreviations: PO = per os, PV = per vagina, Tx = treatment

*See relevant section for more detail and other treatment options

Appendix 1: Equality Impact Assessment

Impact Assessment				
Guideline Title: BASHH Guidelines for the Management of Vulvovaginal Candidiasis 2019 (Completed by Dr Cara Saxon 10/02/2019)				
How relevant is the topic to equality?	Inequalities in health impact of the condition or public health issue	Potential of guidance to add value	Priority for NHS or other government department	Topic relevance: conclusions and outcome
	<ul style="list-style-type: none"> - Prevalence and impact of condition or public health problem - Prevalence of risk factors 	<ul style="list-style-type: none"> - Inequalities in access, uptake or impact - Timeliness - Equality issues identified by proposers of this topic - Equality issues identified by patient or lay organisations 	<ul style="list-style-type: none"> - Department of Health - DCLG, DCSF, DoT, Home Office, etc. - Other agency or ALB - Agencies in devolved nations 	<ul style="list-style-type: none"> - High/medium/low/ none - Not known/ inconclusive - Reasons for rating - Recommendation
Gender <ul style="list-style-type: none"> - Women - Men 	This guideline only covers the condition vulvovaginal candidiasis (VVC). Penile genital candida infection is covered in the BASHH guideline Balano-posthitis 2008	Guideline confirms that candida infection is not sexually transmitted, treatment of sexual partners is not required.	Society of Sexual Health Advisers (SSHA)	Low
Race <ul style="list-style-type: none"> - Asian or Asian British - Black or Black British - People of mixed race - Irish - White British - Chinese - Other minority groups not listed 	VVC is not specifically linked to race. Risk factors for VVC may be linked to race (e.g. diabetes mellitus, HIV)	Guideline covers VVC in diabetes, HIV.	Department of Health	Low
Disability <ul style="list-style-type: none"> - Sensory - Learning disability - Mental health - Cognitive - Mobility 	There are no data to suggest any link between this condition and disability status	None identified although reference to clinical signs and use of clinical tests in guideline may improve diagnostic accuracy in non verbalising patients	Department of Health FSRH	Low

- Other impairment				
Age - Older people - Children and young people - Young adults	VVC is hormonally linked affecting women of reproductive age and typically resolving after the menopause (except in the setting of HRT)	Accurate diagnosis, better understanding of link with hormones (including contraception and HRT) and tolerable treatment should improve burden of disease in the community.	Department of Health	Medium
Sexual orientation and gender identity - Lesbians - Gay men - Bisexual people - Transgender people	This guideline only covers the condition VVC. Penile genital candida infection is covered in the BASHH guideline Balano-posthitis 2008.	Guideline confirms that candida infection is not sexually transmitted, treatment of sexual partners is not required.	Dept of Health Commissioners of local sexual health services	Low
Religion / belief	There are no data to suggest any link between religion or belief and this condition	None identified	None identified	Low
Socioeconomic status	There are no specific data to suggest any link between this condition and socioeconomic status.	None identified	Commissioners of local sexual health services National public health agencies that consider data collection in sexual health (e.g. Public Health England)	Low
Other categories - Gypsy travellers - Refugees and asylum seekers - Migrant workers - Looked after children - Homeless people	There are no data to suggest any link between this condition and these categories.	None identified	Commissioners of local sexual health services National public health agencies that consider data collection in sexual health (e.g. Public Health England)	Low