Guidelines

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

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**SAGE** 

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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 environments and clinical resistance may occur despite the isolate being microbiologically susceptible.

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- 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 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-pri mary-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<sup>+</sup>
  - 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. One thousand four hundred and twelve citations were identified.
- 2. 2007 UK National Guidelines on the Management of Vulvovaginal Candidiasis.

<sup>+</sup> 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 randomized 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 online Appendix 1.

## Piloting and 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 five years.

## Definitions

## Acute VVC

- First or single isolated presentation of 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 four episodes per 12 months with two 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.

VVC is caused by:

- C. 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.<sup>2,4–7</sup> There is no evidence for emergence of non-*albicans Candida* species inherently resistant to azoles.<sup>3,8</sup> There remains conflicting evidence on the virulence and pathogenicity of non-*albicans Candida* species compared with *C. albicans*.<sup>9,10</sup>

An estimated 75% of women will have at least one lifetime episode of VVC, and 40–45% will have two or more episodes.<sup>11</sup> Previous studies have reported that approximately 6% of women of reproductive age will develop recurrent disease.<sup>12,13</sup> 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.<sup>14</sup>

## 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*.<sup>15</sup> For many women an identifiable host factor is not found but can include:

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

On other mucous membranes IL-17-mediated immune responses may be crucial, but this may not be the case in the vagina.<sup>23</sup> Symptoms of VVC are correlated with fungal burden and neutrophil infiltration is involved with symptom production.<sup>24,25</sup> This may relate to the identified link to allergy (allergic rhinitis, asthma and hay fever)<sup>19,26</sup> 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.<sup>19</sup> 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 VVC<sup>29</sup>; however, a more recent study suggests a possible link between iron deficiency anaemia and recurrent VVC.<sup>30</sup> 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.<sup>29,31</sup>

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, whilst the risk of recurrent VVC is also increased for women carrying the allele B homozygote genotype.<sup>32–34</sup>

## **Clinical features**

VVC typically presents with<sup>35–39</sup>:

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

Other symptoms can include<sup>35,38–40</sup>:

- soreness or burning
- superficial dyspareunia
- cyclical symptoms.

Clinical signs may include<sup>35–40</sup>:

- 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.<sup>40,41</sup> Although *C. 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.<sup>41,42</sup> Health-related quality of life both physical and psychological is significantly affected in recurrent VVC.<sup>38</sup>

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.<sup>43</sup>

#### Differential diagnoses and colonization

- Many women (more than half of self-diagnosed women in one study<sup>44</sup>) presenting with these symptoms may have other conditions such as:
  - o dermatitis/eczema
  - o lichen sclerosus

- o other infections (such as herpes simplex, *Trichomonas vaginalis*)
- $\circ$  vulvodynia
- $\circ$  aerobic vaginitis
- o cytolytic vaginosis
- The preponderance of certain symptoms and signs, whilst not pathognomonic can be more suggestive of other conditions (Tables 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<sup>45,46</sup>
- Aerobic vaginitis should be considered if the primary complaint is of a purulent non-offensive discharge<sup>47</sup>
- Cytolytic vaginosis can present with very similar clinical features including curdy discharge and pruritus but microscopy and fungal cultures are negative<sup>48,49</sup>
- Up to 20% of women during reproductive years may be colonized with *Candida* spp. but have no clinical signs or symptoms<sup>50,51</sup>; 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 colonization with *Candida* which is not necessarily contributing to the symptoms.

## Diagnosis

- 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<sup>41,52–57</sup> (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.<sup>24,58-60</sup> (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

	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 <sup>b</sup>	No <sup>6</sup>	Possible, but this is exudate from inflamed skin, not a true discharge	No <sup>b</sup>
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

Table I.	Clinical	features	of vulvovaginal	l candidiasis and	l common	differential	diagnoses – symp	otoms. <sup>a</sup>

<sup>a</sup>The symptoms and signs listed in this table are not pathognomonic 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.

<sup>b</sup>Unless dual pathology.

- Women presenting with features suggesting recurrent VVC should always have a clinical examination<sup>61</sup> (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<sup>62</sup> (Grade 1C)
- Empirical treatment for acute VVC based on the reported symptoms may be given in non-specialist settings<sup>63</sup>; if the symptoms do not resolve, or if they recur, examination and microbiological testing (as below) should be performed.<sup>61</sup>

## 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 colonization.

## Culture

## Acute VVC:

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

Recurrent VVC:

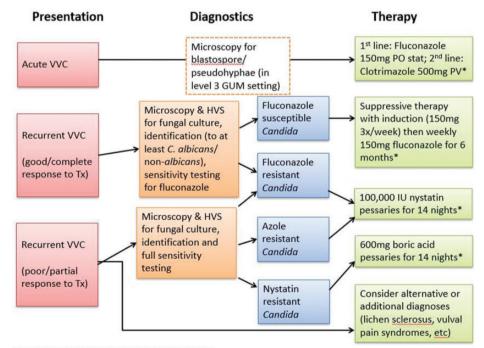
• An HVS of the discharge should be taken for direct plating onto solid fungal growth medium (Sabouraud plate). The benefit of direct plating is

	VV candidiasis	Lichen sclerosus	Vulvodynia	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 <sup>b</sup>	No <sup>b</sup>	Possible, but this is exudate from inflamed skin, not a true discharge	No <sup>b</sup>
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

#### Table 2. Clinical features of vulvovaginal candidiasis and common differential diagnoses – signs.<sup>a</sup>

<sup>a</sup>The symptoms and signs listed in this table are not pathognomonic 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.

<sup>b</sup>Unless dual pathology.



\*See relevant section for more detail and other treatment options

**Figure I.** Summary of the VVC diagnostic and management pathway. HVS: high vaginal swab; PO: per os; PV: per vagina; Tx: treatment; VVC: vulvovaginal candidiasis. \*See relevant section for more detail and other treatment options.

that it enables some level of quantification of *Candida* in the sample.

reliable for samples kept in transport medium for more than 12 h due to continued growth.

- 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
- Any fungal growth should ideally be identified to species level, or at least as *C. albicans*/non-*albicans Candida*<sup>24,58-60</sup> (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 laboratory<sup>64</sup>
- Self-collected swabs done at home can be considered in recurrent VVC where initial samples collected in clinic have come back negative<sup>65,66</sup> (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 and colonization' section).

#### Interpretation of antifungal 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.<sup>67,68</sup>
- In cases of VVC, the vaginal pH is usually in the range of 4–4.5, therefore, isolates with elevated MICs are unlikely to respond to standard doses of azole treatment despite still designated as susceptible:
  - $\circ$  For example, *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*.<sup>69–71</sup> 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 colonization 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 an 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-test ing-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 moisturizer 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 STI. 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 nonbreathable fabric<sup>17,72,73</sup> (Grade 2C)
- using intermenstrual or daily panty liners<sup>73-76</sup> (Grade 2C)
- vaginal douching<sup>22,73,77,78</sup> (Grade 2C)

Vulval emollients may give symptomatic relief as vulval dermatitis (eczema), both primary and secondary, is commonly present.<sup>79</sup>

An association between sexual intercourse and *Candida* colonization levels or vaginal symptoms has not been identified although there is a paucity of research in this area.<sup>80</sup> 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 MBL deficiency can be considered if there are additional clinical indicators (e.g. history of recurrent upper respiratory tract infections or otitis media, autoimmune conditions)<sup>81</sup> (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.<sup>33</sup> 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 150 mg as a single dose, orally (1B)

Recommended topical regimen (if oral therapy contraindicated):

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

Alternative regimens:

- Clotrimazole vaginal cream (10%) 5 g as a single dose, intravaginally\*\* (1B)
- Clotrimazole pessary 200 mg intravaginally at night for three consecutive nights\*\* (1C)

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

Treatment choice:

Studies and data published over the past ten years on the treatment of acute 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<sup>82,83</sup> (Grade 1B)
- Intravaginal imidazoles and oral azoles are equally effective and tolerable in the management of acute VVC with no difference in treatment outcomes<sup>83–86</sup> (Grade 1B)
- Recommended and alternative regimens have been made for this guideline update based on differences in cost and convenience of dosing (fluconazole 150 mg 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 200 mg (for six days) at clinical cure at seven days<sup>84</sup> (Grade 1C)

Treatment considerations:

- \*Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding<sup>51,72,83</sup> (Grade 1B); topical imidazoles are a safe and effective alternative in these situations (see 'Pregnancy and breastfeeding' section)<sup>87,88</sup>
- \*\*Intravaginal and topical treatments can also damage latex condoms and diaphragms with case reports of unplanned pregnancies<sup>84</sup>; 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 metabolized via the cytochrome P450 (CYP) 3A4, such as cisapride, astemizole, pimozide, quinidine and erythromycin, is contraindicated in patients receiving fluconazole.

## Severe VVC

Recommended regimen:

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

Alternative regimens:

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

In patients with severe VVC (i.e. extensive vulval erythema, oedema, excoriation and fissure formation)<sup>89</sup> regardless of a history of recurrence, fluconazole 150 mg should be repeated after three days as this improves symptomatic response but does not influence the risk or rate of recurrence.<sup>90</sup> (Grade 1B) There is no benefit of a seven-day topical treatment course over a single oral dose of fluconazole.<sup>91</sup> If oral treatment is contraindicated it is more logical to repeat a single dose pessary after three days. Two doses of clotrimazole 500 mg vaginal tablet or miconazole nitrate vaginal suppository 1200 mg were as effective as two doses of an oral fluconazole 150 mg regimen in the treatment of patients with severe VVC.<sup>92,93</sup> (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.<sup>94</sup> (Grade 2D)

#### Recurrent VVC

Recommended regimen:

- Induction: fluconazole 150 mg orally every 72 h × 3 doses\* (1A)
- **Maintenance:** fluconazole 150 mg orally once a week for six months\* (1A)

Alternative regimens:

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

\*Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding<sup>51,72,83</sup> (Grade 1B)

#### Treatment choice:

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

- Fluconazole 150 mg every 72 h for three doses followed by 150 mg weekly for a six-month period has been shown to have good efficacy and tolerability in two randomized controlled trials achieving clinical remission in 82–90%<sup>95</sup> (Grade 1A)
- Fluconazole reduced the frequency of recurrent VVC in 88% immediately after the cessation of therapy, 64% at three months after and 61% at six months after the end of treatment<sup>95</sup>
- 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 crossresistance 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 twiceweekly fluconazole 150 mg orally; (Grade 2C) alternatively consider the addition of cetirizine 10 mg od

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

NAC: non-albicans Candida; PO: per os; PV: per vagina; VVC: vulvovaginal candidiasis.

<sup>a</sup>Creams and pessaries may damage diaphragms and latex condoms.

<sup>b</sup>Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding (1B).

or an alternative antihistamine particularly if there is a history of allergy  $^{96}$ 

- Evidence does not support the use of low dose protracted regimens such as fluconazole 50 mg od for 14–28 days for recurrent VVC and suggests there is potential for development of antifungal resistance<sup>97</sup>
- There is a low risk of idiosyncratic drug-induced hepatitis with oral azoles, although fluconazole is less frequently associated with hepatotoxicity than itraconazole (see 'Reactions to treatment' section);
- Oral ketoconazole is no longer recommended for the treatment of fungal infections due to the risk of hep-atotoxicity outweighing the potential benefits.<sup>98</sup>

Treatment duration:

There are no trials addressing the optimal duration of suppressive therapy with the majority of trials using six 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 six months and 77% of women at 12 months using an individualized reducing regimen of fluconazole.<sup>99</sup> However, it is not clear how this strategy compares to the standard six-month regimens. A study comparing these strategies is required before recommendations on reducing regimens can be made.

#### Topical cream:

The roles of anogenital persistence of *Candida* and the use of topical creams in recurrent VVC remain 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 four weeks resulted in a recurrence rate of 34% at 12 months.<sup>37</sup> 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 and colonization' section).

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<sup>39</sup>: 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).<sup>100</sup> 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 100,000 units intravaginally at night for 12–14 consecutive nights (1B)

Alternative regimens:

- Boric acid vaginal suppositories 600 mg daily for 14 days\* (1B)
- Amphotericin B vaginal suppositories 50 mg once a day for 14 days (2C)
- Flucytosine 5 g cream or 1 g 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 100,000 units intravaginally at night for 14 nights per month for six months (2C)
- Consider 14 days per month for six months of the alternative regimens (2D)

Antifungal susceptibility:

- *C. 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 *C. glabrata* and *C. krusei*:
  - these can be the sole cause of infection or in combination with *C. albicans*
  - $\circ$  most vaginal *C. glabrata* strains are reported as susceptible to azoles<sup>101</sup> but with elevated MICs and often with poor clinical response to standard dose treatment

 $\circ$  C. krusei is intrinsically resistant to fluconazole<sup>102</sup>

- 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 are 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 h for one 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.<sup>51,103</sup> They are the only licenced alternative to azole therapy.
- Boric acid vaginal suppositories 600 mg daily for 14 days are a safe and effective alternative.<sup>101,104,105</sup> (Grade 1B) If mucosal irritation occurs the dose can be reduced to 300 mg daily (additional cost likely as it needs to be compounded specially).<sup>106</sup> There may be a teratogenic risk so boric acid should be avoided in pregnancy or risk of pregnancy.<sup>107</sup>
- Amphotericin B vaginal suppositories 50 mg once a day for 14 days has a 70% success rate.<sup>108</sup> (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.<sup>8,101,109</sup> (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 pregnancies<sup>84</sup>; 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 fluconazoleresistant *Candida* species, 14 days of nystatin pessaries a month for six months has been shown to be effective and is more likely to achieve mycological cure than fluconazole regimens.<sup>110</sup> (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 six months to the alternative options. (Grade 2D)

#### Pregnancy and breastfeeding

Recommended regimens (acute VVC in pregnancy):

• Clotrimazole pessary 500 mg intravaginally at night for up to seven consecutive nights\* (1C)

#### Alternative regimens (acute VVC in pregnancy):

- Clotrimazole vaginal cream (10%) 5 g intravaginally at night for up to seven consecutive nights\* (1C)
- Clotrimazole pessary 200 mg intravaginally at night for up to seven consecutive nights (1C)
- Econazole pessary 150 mg intravaginally at night for up to seven consecutive nights (1C)
- Miconazole capsule 1200 mg\* or 400 mg intravaginally at night for up to seven consecutive nights (1C)
- Miconazole vaginal cream (2%) 5 g intravaginally at night for seven 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%.<sup>111</sup> (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 500 mg pessary or 10% cream, miconazole 1200 mg) 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 500 mg 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 colonization with *Candida* species is more common  $(30-40\%)^{112}$  and symptomatic candidiasis is more prevalent throughout pregnancy
- Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding<sup>51,72,83</sup> (Grade 1B)
- Topical imidazoles are safe and effective for symptomatic VVC in pregnancy and breastfeeding<sup>87,88</sup> (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 150 mg fluconazole but should be avoided after repeated or high doses of fluconazole<sup>113</sup>
- 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<sup>114</sup>

- 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 dtransposition of the great arteries although overall fluconazole use in the NBDPS was low<sup>115</sup>
- 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 and 22 weeks' gestation compared with risk among unexposed women and women with topical imidazole exposure in pregnancy<sup>87</sup>
- A preliminary study in Denmark with 812 motherson pairs found that fluconazole exposure in four pregnant women was significantly associated with shorter anogenital distance suggesting a potential anti-androgenic effect.<sup>116</sup>
- 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.<sup>117</sup>

VVC and pregnancy outcome:

- Previous studies did not find evidence of an association between *Candida* colonization and premature delivery or low birth weight.<sup>112,118</sup>
- There remains insufficient evidence of an association between detecting asymptomatic VVC in pregnancy and the risk of pre-term birth or low birth weight<sup>119–</sup> <sup>124</sup>; well-designed studies in this area are warranted.

## Alternative or supplementary treatments

Some evidence of benefit:

- Anti-allergy:
- $\circ$  Cetirizine 10 mg orally daily for six months may cause remission in women who fail to get complete resolution of symptoms with suppressive fluconazole<sup>96</sup> (Grade 2C)
- Zafirlukast 20 mg orally twice daily for six months may be considered as maintenance prophylaxis for recurrent VVC, particularly in women with a history of atopy<sup>125</sup> (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<sup>84,126</sup>
  - The mode of action might be via modulation of inflammatory processes rather than competition with *Candida*.<sup>127</sup>
- Tea tree and other essential oils: are antifungal in vitro but they may cause hypersensitivity reactions.<sup>84,128</sup> There is insufficient evidence to recommend use in recurrent VVC.<sup>84</sup>
- 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.<sup>129</sup>
- **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.<sup>130,131</sup>
- **Diet:** there is no evidence to support any dietary modifications, including reducing carbohydrate or yeast intake.<sup>94,132</sup>
- **Oral garlic:** there is no evidence of benefit from oral garlic on *Candida* colonization.<sup>133</sup> Observational studies have shown that garlic taken orally may cause heartburn, nausea, diarrhoea, flatulence, bloating and an offensive body odour.<sup>84</sup>

#### Diabetes mellitus

#### **Recommendations:**

- Known diabetic women with poor glycaemic control should be encouraged to improve this
- Fluconazole 150 mg orally as a single dose for confirmed *C. albicans* in diabetic women with acute VVC (1C)
- Treat as per the recommendations above for nonalbicans 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*.<sup>134–136</sup>

In diabetic women with symptomatic VVC where *C. albicans* is isolated, single-dose fluconazole (150 mg) gives a similar response to non-diabetics.<sup>135</sup> (Grade 1C) In diabetic women with symptomatic VVC due to *C. glabrata*, treatment with boric acid 600 mg pessaries intravaginally at night for 14 consecutive nights achieved a higher mycological cure rate at 15 days compared to fluconazole 150 mg orally as a single dose.<sup>137</sup> 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 interactions between antifungals and antiretrovirals.

VVC occurs more frequently and with greater persistence in HIV-infected women.<sup>138,139</sup> Increased HIV shedding in the vagina, plasma HIV load above 1000 copies/ml, CD4 lymphocyte count below 200 cells/mm<sup>3</sup> and the absence of antiretroviral therapy have been associated with an increased risk of symptomatic VVC.<sup>35,139</sup> 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.<sup>140</sup> (Grade 1C)

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

#### 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 combined oral contraceptive (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 puber-tal/post pubertal and not pre-pubertal females.<sup>141</sup> 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.<sup>20</sup>

There is some evidence that 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.<sup>18,142,143</sup> 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.<sup>144,145</sup>

In theory, certain progestogen-only methods (desogestrel progestogen-only pill [POP], progestogen-only implant, depot medroxyprogesterone acetate) 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).<sup>18</sup> One observational study reported a significant lower Candida carriage rate in users of the progestogen-only implant and POP than users of the copper intrauterine device (Cu-IUD) or levonorgestrel intrauterine system (LNG-IUS).<sup>143</sup> 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.<sup>146</sup>

The Cu-IUD has been identified as a possible risk factor for both acute and recurrent VVC.<sup>147</sup> There is some evidence that *Candida* can adhere to a Cu-IUD and produce a biofilm.<sup>148,149</sup> 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.<sup>143,150–153</sup>

## 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 and treatment**

There is no evidence to support the treatment of asymptomatic male sexual partners in acute or recurrent VVC.<sup>154–157</sup> (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 nonpregnant 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 two (of the  $\geq$ 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 who have a recurrence of symptoms after completing six months of treatment for recurrent VVC
- Further assessment of the benefit of treating asymptomatic colonization 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).

## **Editorial independence**

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

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