

Guideline: Vulvovaginal candidosis (AWMF 015/072, level S2k).

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distribution in any medium, provided the original work is properly cited, the use is non-commercial
and no modifications or adaptations are made. Abstract Approximately 70–75% of women will have
vulvovaginal candidosis (VVC) at least once in their lifetime. In premenopausal, pregnant,
asymptomatic and healthy women and women with acute VVC, *Candida albicans* is the
predominant species. The diagnosis of VVC should be based on clinical symptoms and microscopic
detection of pseudohyphae. Symptoms alone do not allow reliable differentiation of the causes of
vaginitis. In recurrent or complicated cases, diagnostics should involve fungal culture with species
identification. Serological determination of antibody titres has no role in VVC. Before the induction
of therapy, VVC should always be medically confirmed. Acute VVC can be treated with local
imidazoles, polyenes or ciclopirox olamine, using vaginal tablets, ovules or creams. Triazoles can
also be prescribed orally, together with antifungal creams, for the treatment of the vulva. Commonly
available antimycotics are generally well tolerated, and the different regimens show similarly good
results. Antiseptics are potentially effective but act against the physiological vaginal flora. Neither a
woman with asymptomatic colonisation nor an asymptomatic sexual partner should be treated.
Women with chronic recurrent *Candida albicans* vulvovaginitis should undergo dose-reducing

maintenance therapy with oral triazoles. Unnecessary antimycotic therapies should always be avoided, and non-*C. albicans* vaginitis should be treated with alternative antifungal agents. In the last 6 weeks of pregnancy, women should receive antifungal treatment to reduce the risk of vertical transmission, oral thrush and diaper dermatitis of the newborn. Local treatment is preferred during pregnancy.

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Vulvovaginal candidosis (VVC) is a common reason for consultation in gynecological offices. 1 , 2 In addition to its high prevalence, VVC causes a high level of distress in an affected patient. 3 Surveys reported that 70–75% of women will develop VVC at least once during their lifetime. The disease can be promoted or induced by various factors, including host factors, local defence mechanisms, gene polymorphisms, allergies, serum glucose levels, antibiotics, psychosocial stress, oestrogens and sexual activity. 4 However, most episodes do not have a single definable trigger. 5 , 6 The oestrogenised vagina is colonised by *Candida* species (spp.) in at least 20% of pregnant women and 30% of immunocompromised patients, if examined via a culture. When non-culture methods are used, fungi can be found in > 60% of cases. 7 The predominant species is *Candida albicans* , followed by non-*C. albicans* species, such as *C. glabrata* , *C. tropicalis* , *C. krusei* and *C. parapsilosis* . 8 Infections with non-*C. albicans* species are often accompanied by milder symptoms than those in vaginitis caused by *C. albicans* . Non-*C. albicans* vaginitis is more likely to develop during pregnancy, following antibiotic therapy, or in women with increased oestrogen levels, for example during hormonal replacement therapy or oral contraceptive use. 5 In women with acute VVC, several treatment options with equivalent therapeutic success are available. However, infections that are induced by *Candida glabrata* and other non-*C. albicans* species are often nonresponsive to usual doses and first-line antimycotics. Therefore, these situations warrant alternative treatment recommendations, although some agents might be difficult to acquire (e.g., from international pharmacies) or are not officially approved for this indication. This is the official English translation of the guidelines of the German, Austrian and Swiss Societies of Gynecology and Obstetrics, which aimed to evaluate the scientific evidence and clinical practice experience for the diagnosis and treatment of VVC. Herein, we aimed to clarify conflicting points and statements and recommendations that are based on an interdisciplinary consensus, considering the advantages and disadvantages of each measure.

We performed a MEDLINE/PubMed literature search with the keyword 'vulvovaginal candidosis', which resulted in 3901 titles as of May 2020. A literature search using 'vulvovaginal candidosis therapy studies' resulted in 450 papers. All studies were searched by title and abstract, leading to only a few prospective or randomised controlled trials. Seven meta-analyses 2 , 9 , 10 , 11 , 12 , 13 , 14 and four published guidelines were found, 15 , 16 , 17 , 18 two of which were preliminary versions of this guideline. A systematic evaluation of the literature and extraction of evidence tables were performed for the classification S2k. The available literature was critically evaluated by the authors of this guideline. For details on the consensus procedure, patient involvement, evaluation and handling of potential conflicts of interest, participation of different professional societies, and validity period, please refer to the guideline report, which can be found in the extended full text of the German version of this guideline, as presented in the Acknowledgments section.

VVC is an infection of the primarily oestrogenised vagina and vestibule that can spread outside the small labia, large labia, and intercrural and perianal regions. There is no candidosis of the cervix or endometrium. Congenital foetal candidosis and *Candida* amnionitis have been reported but are extremely rare. The terms 'candidosis' and ' *Candida albicans* vulvovaginitis' are preferred, 19 whereas the suffix '■iasis' should only be used for parasitic infections (e.g., trichomoniasis). 20 The term 'candidiasis' is often used because of its wide distribution in Anglo■American literature, although it should be avoided. The appropriate consensus■based recommendation #1 is presented in Table 1 .

Consensus■based recommendations and statements

+ = <75% consensus; ++ = 75■95% consensus; +++ = >95% consensus.

John Wiley & Sons, Ltd 4 MICROBIOLOGY In vitro, *Candida albicans* forms blastospores, germ tubes, pseudohyphae, true mycelia and chlamydospores on special nutrient media. *Candida glabrata* only forms blastospores. Generally, the formation of pseudohyphae is a sign of infection, except for *C. glabrata* and other *Candida* spp., which commonly form blastospores. 1 , 21 *Candida* spp. differ in vitro in their pathogenicity so that candidosis can develop differently depending on the species and strength of the host defence mechanisms. 22

In premenopausal, pregnant, asymptomatic and healthy women and women with acute VVC, *C. albicans* is the predominant species. This species is similar to *C. africana* but can only be identified by special diagnostic procedures. 23 , 24 Although there are regional differences in the distribution of the *Candida* spp. (Tables 2 , 3 , 4), studies from German■speaking 25 , 26 and English■speaking countries 26 report comparable numbers. In a retrospective PCR■assisted analysis of 93,775 cervicovaginal smears that were collected for VVC testing, *C. albicans* showed a prevalence of 89%, whereas *C. glabrata* was identified in 9% and other species were identified in < 2% of the observed cases. 27

Candida colonisation of the vagina in HIV■positive or HIV■negative women 129

John Wiley & Sons, Ltd TABLE 3 *Candida* species in patients with positive vaginal culture 129

John Wiley & Sons, Ltd TABLE 4 Distribution of *Candida* species in women with acute VVC in Europe 25

John Wiley & Sons, Ltd Non■ *albicans* species, particularly *C. glabrata* , are more commonly observed in postmenopausal, diabetic and immunocompromised women. 28 , 29 , 30 , 31 , 32 , 33 *C. krusei* , *C. guilliermondii* , *C. tropicalis* , *C. parapsilosis* and others can cause vulvovaginitis with typical symptoms, 1 , 34 , 35 , 36 whereas *Saccharomyces cerevisiae* is apathogenic and does not cause any symptoms. 21 , 37 The latter can be identified as a commensal in 1■2% of all vaginal cultures (Tables 3 and 4). 32

In asymptomatic women and those with acute *Candida* vaginitis, different genotypes of *C. albicans* have been identified. 38 Identical strains of *C. albicans* have been detected by molecular biological methods, in both the orointestinal and vaginal tracts of a woman and sperm of the asymptomatic partner. 39 In addition, *C. dubliniensis* has increasingly been isolated in the orointestinal and vaginal tracts of women with VVC, as it is a species that is closely related to *C. albicans* (statement #2, Table 1). 40 , 41

Apart from the virulence of the pathogen, the pathogenesis of VVC depends on the individual predisposition and defence mechanisms of the host. On one hand, yeasts are typical opportunists that cause infection in case of a weak local host defence (e.g., oral thrush in HIV■positive patients). On the other hand, most women who have VVC are otherwise healthy. To date, it is still unclear why a simple colonisation by *Candida* spp. results in an acute and highly inflammatory infection.

The importance of host factors is demonstrated by the step from colonisation to vaginitis. 42 Based on colonisation, adherence to the vaginal epithelium occurs, followed by invasion, infection and inflammation by means of virulence factors. Some *Candida* virulence factors (e.g., proteases, lipases and candidalysin) enable yeasts to induce infection. The formation of pseudohyphae results in the formation of fungal components that stimulate a violent chemotaxis of granulocytes, which then cause inflammation. 43 Candidalysin plays a role in this process, since it is a peptide toxin of *C. albicans* that has a cytotoxic effect on the host cells, promotes invasion, recruits leucocytes 44 , 45 and stimulates the nonspecific defence against infection. 46

Mannoproteins allow the adherence of *Candida* cells to the vaginal wall. 47 , 48 , 49 The ability to form pseudohyphae and secretion of hydrolytic proteins, such as secretory aspartate proteinases (Sap 1-10), are probably the most important virulence factors in this context 50 , 51 , 52 and correlate with *Candida*'s pathogenicity. 53 , 54 Siderophores allow the use of iron of the host. 55 , 56 Other factors include pH tolerance 57 and presence of enzymes that allow *C. albicans* to survive in macrophages. 58 Cytological observations indicate that pseudohyphal filaments dominate yeast cells at a vaginal pH level of 4.0-5.0, together with the co-expression of typical hyphal-associated genes. 59

In an acute infection, inflammasome receptors of the vaginal epithelial cells are activated by the formation of virulence and immune inflammation factors. Fungal components, such as glucan, mannan and chitin, bind to specific receptors of macrophages and stimulate various cytokines. 60 Beta-glucan binds to dectin-1 and stimulates the release of proinflammatory cytokines. 60 This, in turn, leads to the activation of innate immunity and NLRP3 inflammasome, 59 which is important in the development of VVC. 61 , 62 , 63

Biofilms protect the fungi and help them live symbiotically with others in a matrix substance. 64 Auler et al 65 and Chassot et al 66 described the biofilm phenomenon of *C. albicans* in intrauterine pessaries. Muzny and Schwabke reported similar observations. 64 However, it is still unclear when *Candida* behaves like a pathogen rather than a coloniser, which then contributes to the change from commensalism to a pathogenic state. 64

One of the requirements for the invasion of *Candida* is the transition from the yeast to the hyphal form, which is promoted by the presence of oestrogens, due to the fact that fungi contain cytoplasmic oestrogen receptors. 67 When these oestrogen receptors are stimulated, the pathogenicity and virulence of *Candida* increases, clarifying why women of childbearing age are more likely to have VVC, particularly during hormonal contraception and pregnancy. 62 , 64 The appropriate consensus-based statement #3 is given in Table 1 .

Due to reduced oestrogenisation of the vagina, premenstrual girls and postmenopausal women, in the absence of hormonal replacement therapy, are less likely to develop *Candida* colonisation. 68 , 69 It has been demonstrated in animal studies that VVC only developed in castrated animals following oestrogen replacement. In contrast, the vaginas of approximately 20-30% of healthy, non-pregnant and premenopausal women are colonised by *Candida* (statement #4, Table 1).

There is no clear evidence for the increasing incidence of VVC, for neither the acute nor the chronic recurrent disease. It is known that the vaginas of approximately 30% of women who are in the third trimester of pregnancy are colonised by *Candida* . The vaginas of women with immune deficiencies are more likely to be colonised, as has been reported from studies that used culture methods (Tables 2 and 3). 33 The use of PCR significantly increases the detection of vaginal *Candida* colonisation. 70 However, it should be considered that there are changes in vaginal colonisation and that positive results for certain species are mostly a sign of colonisation but not of infection. For instance, a longitudinal cohort study that evaluated the vaginal microbiota of 1248 asymptomatic healthy young women showed that 70% were colonised by *Candida* spp. at least once over a period of one year and that only 4% of these women showed *Candida* colonisation during the

follow-up visits every three months. Recent sexual intercourse, medroxyprogesterone acetate (MPA) injection, and lactobacilli and Group B streptococcus colonisation were identified as risk factors for *Candida* colonisation in this study. 71

Although men are mostly free of symptoms, their sperm might also be colonised with the identical *Candida* spp. that can be found in the vagina of their sexual partner. 39 *Candida* balanitis should be treated, but the temporary redness of the glans penis after intercourse with a female partner with *Candida* colonisation might also just be reactive. It is still unclear whether the colonisation of the partner's genital or orointestinal tracts is a potential source of chronic recurrent *Candida* vaginitis. 1 , 72 If this is the case, it could be one explanation for the relatively low eradication rate of 62% after antimycotic therapies, apart from the high genetic heterogeneity of the *C. albicans* genotypes. Moreover, it has been shown that *C. albicans* persists for approximately 1-2 months after therapy, which is probably less attributable to specific genotypes than to an increase in the minimum inhibitory concentration (MIC). 73

In Germany, 70-75% of healthy women will have VVC at least once during their lifetime, corresponding to approximately 3619 per 100,000 women aged 15-54 years. 6 Many of them have > 4 episodes per year, which is defined as recurrent VVC (RVVC). 1 , 31 In an Internet survey on 6,000 women in five European countries and the United States, 30-50% of women reported that they had VVC and 9% had RVVC for several years. 74 In the following, we described some underlying mechanisms for predisposing host factors, including diabetes, antibiotic use, vaginal microbiota, hormonal factors including contraceptive use, and genetic and lifestyle factors (Statement #5, Table 1).

Patients with diabetes mellitus and high serum glucose levels are more likely to have VVC and not respond to antimycotic therapy. 28 , 75 This relationship is controversial in pregnant women. 76 Gestational diabetes (GDM) is associated with impaired metabolic control, higher body mass index and impaired leucocyte function. 6 , 77 In addition, a correlation between GDM and altered vaginal flora has been established. 43 , 44 , 45 , 46 , 78 , 79 Glycaemia in vaginal tissue increases fungal adhesion and growth and predisposes vaginal epithelial cells to bind to yeast. In addition, a glycaemic index of 10-11 mmol/L can impair the host's defence mechanism. Hyperglycaemia decreases neutrophil migration and weakens their chemotactic and phagocytic powers, thereby increasing their sensitivity to VVC. 6 , 77 During pregnancy, both GDM and abnormal vaginal flora have been associated with poor pregnancy outcomes. 76 *Candida* -induced infections appear to be more commonly associated with GDM. In addition, associations between the abnormal vaginal flora and incidence of preterm premature rupture of the membranes, preterm delivery, chorioamnionitis and postpartum complications have been reported in women with GDM. 80 Women with chronic RVVC have also shown a lower glucose tolerance compared to healthy controls. 81 Obesity, combined with intertrigo through chafing and sweating, is also thought to contribute to VVC.

Candida glabrata is less virulent than other species, but women with type II diabetes mellitus have shown more frequent colonisation with *C. glabrata* compared with healthy women. 30 , 82 Antidiabetic SGLT2 inhibitors (e.g., dapagliflozin and canagliflozin) increase not only glycosuria but also the number of VVC episodes. 5 , 83 , 84 Women with an increased likelihood of developing diabetes mellitus, such as those with cystic fibrosis, also have an increased risk of developing VVC. 85 , 86 In the case of recurrent episodes of VVC in diabetic women, control and discontinuation of antidiabetic medication is appropriate. 44

Women who already have *Candida* colonisation have an increased risk of developing VVC after antibiotic treatment. 87 , 88 , 89 , 90 However, the exact pathogenesis of VVC after antibiotic therapy is still unknown. Clinical experience suggests that antifungal prophylaxis after antibiotic therapy may be considered but does not appear to be generally recommended to avoid the development of resistance. 91 The most commonly prescribed and effective VVC prophylaxis is the intake of fluconazole 150 mg with antibiotics, and fluconazole can be administered either at the beginning or at the end or once weekly during antibiotic treatment. Another option is the

simultaneous intake of oral or vaginal probiotics, which follows the theory that women with VVC have ineffective or reduced vaginal or intestinal lactobacilli. 91

VVC frequently develops in women with a normal vaginal microbiota, but a low number of lactobacilli has been reported in women with VVC than in those without. 92 The diversity of the microbiota seems to be particularly important, although the pattern in VVC is not as clear as that in bacterial vaginosis. 44 , 93 Some lactobacilli also have an antagonistic effect against *Candida* . 94 , 95 This antagonistic effect has been shown for example *Lactobacillus rhamnosus* . 96 , 97 , 98 , 99 , 100 The vaginal administration of *L. rhamnosus* , twice daily for 1 week, after vaginal miconazole or *L. casei rhamnosus* Lcr 35 , has shown sufficient vaginal colonisation and reduction in the VVC recurrence rate within 6 months after treatment. 101 , 102 The protective effect of lactobacilli is mainly due to their ability to adhere to vaginal epithelial cells and inhibit the growth of pathogens. Various mechanisms are used for this purpose, including immune modulation; production of antimicrobial substances, such as organic acids, hydrogen peroxide and bacteriocins; competition for nutrients; and inhibition of adhesion of pathogens to epithelial cell receptors. 103

The glycogen stored in the vaginal epithelium serves as a potential nutrient substrate for *Candida* . 69 Oestrogens are responsible for the formation of inhibitors by epithelial cells, which inhibit the antimycotic function of granulocytes and thus cause leucocyte energy. 43 , 44 , 45 The leucocyte energy in vaginal mycosis is explained by the fact that, under certain circumstances, including high oestrogen levels, epithelial cells produce inhibitors, such as heparan sulphate, which prevent the relevant receptors of the granulocytes from interacting with the corresponding ligands of the yeast. 43 , 45 VVC symptoms are most frequently reported in the middle of the menstrual cycle, due to increased oestrogen levels with high glycogen content, and during the luteal phase, while there is a rapid decline in symptoms following the decrease in oestrogen levels during menstruation. 69 Women using combined oral contraceptives also have higher oestrogen levels, as do postmenopausal women on hormone replacement therapy, and both groups have increased risk of developing VVC. 104 In addition to these factors, the hormonal condition in women may also have a direct influence on the immune response and pathogenicity of *Candida* . 105

Vaginal *Candida* colonisation is usually decreased during intake of low-oestrogen oral contraceptives that do not significantly affect carbon metabolism. 100 , 106 This might show similarity in the frequency of the VVC, although this is still unclear. 107 However, a systematic review has shown an increased risk of VVC during oral contraceptive intake, most likely dependent on the dose of oestrogen. 108 Progestins alone seem to have a protective effect against VVC. 44 , 109 Regarding the use of intrauterine devices (IUD), Donders et al 77 recommend avoiding levonorgestrel-releasing systems (LNG-IUS) in women with RVVC and those with increased risk of VVC. The likelihood of VVC was particularly high within the first year of LNG-IUS use and still significantly increased five years after insertion of the device.

Genetic factors might be responsible for VVC relapse, since genetic polymorphisms of the mannose-binding lectin 110 , 111 and a non-secretor phenotype of the ABO Lewis blood group were both identified as risk factors for VVC relapse. 112 In families with RVVC, some mutations have been described, such as the one responsible for the loss of the last nine amino acids in the carbohydrate recognition domain. The resulting altered form of the lectin, Dectin-1, leads to an insufficient production of cytokines (interleukin-17, tumour necrosis factor, interleukin-6) after stimulation with β -glucan or *Candida albicans* . In contrast, phagocytosis (and thus the killing of the yeast) seems to be unaffected in patients with VVC, which explains why a Dectin-1 deficiency is not associated with VVC. The corresponding mutation for VVC is relatively common in parts of Europe and in Africa, with prevalence rates of 3-7%. 113 Symptomatology occurs earlier in homozygous than in heterozygous mutation carriers.

Since infection equals colonisation plus disposition, immunocompromised individuals more often develop VVC. Factors of congenital and acquired humoral immunity that are believed to neutralise *Candida* spp., to prevent the step from asymptomatic colonisation to adherence and infection, are of interest in this context. Th1-induced dendritic T cells/Langerhans cells are promoted by

interleukin■12. Oral and vaginal epithelial cells are able to differentiate Candida polymorphism (colonising blastospores or infecting pseudohyphae). They produce proinflammatory cytokines that activate neutrophil granulocytes. However, in the vagina, this process is not protective but leads to inflammation.

Immune messengers from the family of type I interferons, known as signalling molecules, which actually control the body's own immune defence in infections, interfere with the correct formation of proteins that remove iron from macrophages in *C. glabrata* infections. If the fungus is now engulfed by a macrophage and absorbed into the phagolysosome, excess iron is accumulated in this organelle, which in turn can be used for fungal growth. One macrophage alone can consume up to 50 fungal cells, which survive for months and spread when the macrophages burst. 7

Antibodies against components of Candida have recently been described, and antibody■producing B cells have been considered protective. 114 , 115 , 116 , 117 , 118 Women with atopic diathesis and type I allergies were more likely to develop VVC than healthy women. 119 The clinical signs of VVC, such as redness and itching, can also be an expression of an allergic phenomenon, particularly in RVVC. 1 , 120 Women with RVVC express heat shock proteins during the symptom■free interval, which can then trigger similar immunological defence reactions as Candida cells. 121 , 122

Sobel has underlined the underestimated role of an individual's sexual behaviour in relapses of VVC 1 and reported that relapses occurred more often after oral sexual intercourse. 90 , 123 , 124 Apart from that, it is known that psychosocial stress might trigger RVVC through immunosuppression. 125 , 126 Conversely, VVC leads to a negative influence on the patient's work and social life. Some experts also consider nutrition as relevant in VVC development, since the consumption of foods that are rich in sugar and carbohydrates and those with high yeast content or dairy products has been associated with increased fungal growth. 81 , 127 Vegetable and protein products can be consumed without any restrictions. Yoghurt might have a positive probiotic effect, and oat bran and linseed have shown antifungal characteristics. 8 However, the available evidence of the effect of nutrition on Candida growth and VVC incidence can generally be considered weak.

Premenopausal women usually have candidosis that affects the vestibulum and vulva, while postmenopausal women are often affected in the groin/inguinal region and vulva. There is no Candida cervicitis. In premenopausal women, symptoms typically occur before the menstrual period, as oestrogen■induced cell proliferation and progesterone■induced cytolysis release glycogen that can be metabolised by lactobacilli, resulting in increased tissue glucose levels. 90

From a clinical perspective, it is recommended to differentiate between complicated and uncomplicated cases of VVC. 1 However, the microscopic identification of pseudohyphae, which would be needed, is not always possible. In approximately 90% of VVC cases, itching is the predominant symptom, although only 35■40% of women who complain of itching actually have VVC (statement #6, Table 1). 70 , 128 , 129 The vaginal discharge can vary in consistency from thin (often at the onset of acute VVC) to flaky, and it can be absent in cases of RVVC. 6 , 130 In contrast to bacterial vaginosis, vaginal discharge does usually not have an unpleasant odour in case of candidosis but usually has a whitish, lumpy consistency. 6

In addition to premenstrual itching in the vulva and/or vagina, most women with VVC complain of vaginal redness, soreness, burning, dyspareunia and dysuria. 6 However, symptoms alone cannot reliably distinguish the different causes of a vaginitis, as itching and redness are not always reported by women with VVC. 131 The labia minora might be oedematous with signs of burning rhagades, especially in cases of RVVC.

VVC symptoms are associated with the presence of extracellular matrix metalloproteinases and, in particular, matrix metalloproteinase■8 (MMP■8). 132 Vestibulodynia, which develops in pronounced cases and persists after successful treatment, is induced by a fibroblast■mediated

proinflammatory immune response. 133

In addition to the typical symptoms of most *C. albicans* induced VVC, *C. glabrata* vaginitis is rare and usually develops in the late pre- or perimenopausal period. 26 , 134 , 135 , 136 , 137 The symptoms caused by *C. krusei* vaginitis 138 and *C. parapsilosis* vaginitis 139 are usually similar to those caused by *C. glabrata* , with mild clinical symptoms. *Saccharomyces cerevisiae* is apathogenic and therefore unlikely to cause vaginitis and symptoms. 21 , 37 , 140

From a dermatological point of view, candidosis of the vulva can be vesicular, eczematous or follicular.¹⁵ Many women with secondary vestibulodynia report VVC before the onset of vestibular pain. An animal study showed a significant association between VVC and vestibulodynia and ingrowth of unusually thick nerves into the superficial epithelial layers, demonstrated by immunohistochemical changes. 141

Symptoms of candida vaginitis, especially in cases of RVVC, lead to a reduction in quality of life, as measured by established evaluation criteria. This reduction is comparable to that of patients with bronchial asthma or chronic obstructive bronchitis and associated with a significantly reduced productivity in their daily work and private life. 142

Despite the presence of *Candida* , the clinical diagnosis of VVC might be difficult, since itching at the introitus is not necessarily caused by *Candida* vaginitis. In a prospective study on the accuracy of the clinical diagnosis of bacterial vaginosis, trichomoniasis and VVC in 535 female soldiers with vulvovaginal complaints, the sensitivity and specificity of the diagnosis with classical diagnostics (history, vaginal examination, pH, microscopy of the native preparation) were 83.8% and 84.8%, respectively, 143 which confirmed the results of previously published studies. 144

For proper diagnosis, the presence of (pseudo-)hyphae is always necessary in the detection of *Candida* vaginitis, particularly to distinguish it from asymptomatic colonisation. Apart from proper anamnesis and gynaecological examination, microscopic examination of vaginal discharge with saline or 10% potassium hydroxide solution using light or phase contrast microscopy with 400 × optical magnification (10 × eyepiece plus 40 × objective) is mandatory. 21 , 145 Measurement of the vaginal pH can also be performed. Blastospores and/or (pseudo-)hyphae can be found during microscopy in 50-80% of vaginal candidosis cases, 1 , 144 whereas they can only be detected in half of the cases during colonisation. An increased number of leucocytes might also be found. If no blastospores or (pseudo-)hyphae can be found during microscopy, it might be that the amount of microorganisms was extremely small, resulting in low sensitivity. However, inflammation can be triggered despite a low fungal load, and therefore, the more sensitive cultural methods should be conducted for identification of species in some cases, for example in patients with chronic RVVC. Since clinical resistance is not correlating with the minimal inhibitory concentration, its determination is considered unnecessary. 90 , 146 , 147

The typical medium for the cultural diagnosis of *Candida* spp. is the Sabouraud-2% glucose agar. Other media that are available for the detection of *Candida* include the CHROMagar TM and Microstix-*Candida* . Chromogenic media can immediately identify certain *Candida* spp. due to their pigmentation and facilitate the detection of mixed cultures in case of simultaneous presence of two or more different yeast species, for example when *C. albicans* and *C. glabrata* are both present. Then, the patient typically develops *C. albicans* vaginitis, while resistant *C. glabrata* remains in situ after treatment. *C. glabrata* is present during colonisation, and there is no need for treatment in the absence of any symptoms. In vitro sensitivity testing is unnecessary, except in chronic cases of non-*C. albicans* vaginitis.

Modern DNA hybridisation tests of vaginal discharge from the speculum of the gynaecological examination have shown sensitivity and specificity rates for the detection of *Candida* of up to 96.3%. 148 Even higher detection rates can be achieved using whole genome sequencing methods. 149 In contrast, serological tests are not considered useful in the diagnosis of VVC. This

is mainly due to the fact that antibody levels can be measured in women with and without VVC (e.g., intestinal colonisation) and that superficial VVC does not cause elevated antibody levels. The appropriate statements and recommendations #7-9 are given in Table 1 .

In immunocompetent patients without evidence for chronic disease, asymptomatic vaginal colonisation does not require any treatment, even in cases with high fungal load. In contrast, symptomatic patients require treatment, and there are numerous options to treat these patients. 150 The following substances can be used to treat VVC: azoles, which hinder the conversion of lanosterol to ergosterol in the cell membrane of the yeast 151 ; polyenes, which form complexes using the ergosterol of the yeast membranes and alter their permeability 152 ; and ciclopiroxolamine, which inhibits important iron-dependent enzymes through chelate formation. 153 In cases of chronic RVVC, dose-reducing suppression therapy with 200 mg oral fluconazole might be considered as follows: three times weekly for one week; followed by once weekly for two months; if symptom- or fungus-free, then twice monthly for four months; and finally once monthly for six months (Figure 1).

Maintenance therapy with fluconazole in patients with chronic RVVC

Acute VVC can be treated locally with topical imidazole derivatives (ie clotrimazole, econazole, isoconazole, fenticonazole, miconazole) at the first manifestation. There are vaginal suppositories and creams available with dosages and preparations for a treatment duration from 1-3 days to 6-7 days. 154 The US Centers for Disease Control and Prevention also recommends tioconazole, butaconazole, and terconazole, which are, however, available to a limited extent on the market in German-speaking countries. 155 Alternative treatment options for non-pregnant women are oral triazoles (ie fluconazole, itraconazole, posaconazole, voriconazole), polyenes (ie nystatin), 1 , 154 , 156 and ciclopiroxolamine. 157 Amphotericin B is a polyene that is not available for vaginal use (Table 5). Treatment success rates are comparable between the different treatment strategies, 158 varying between 85% after 1-2 weeks and 75% after 4-6 weeks. 9 , 25 , 159 , 160 , 161 Local treatment with 500 mg clotrimazole as vaginal tablet or 10% vaginal cream was proven effective as single oral administration of 150 mg fluconazole. 25 Likewise, there is no significant difference in the patients' relief of symptom between different treatments. During pregnancy, treatment with topical imidazole was shown to be more effective than treatment with topical nystatin. 12

Treatment options for patients with acute VVC

John Wiley & Sons, Ltd If VVC affects the vulva outside of the introitus vaginae or inguinal region, an antifungal cream (e.g., clotrimazole) is recommended twice daily for one week. Combined treatment of intravaginal and topical cream for the external genital region and vulva seems to achieve more favourable healing results than intravaginal therapy alone. However, there are only few studies that have proven this. 162 , 163

The necessary amount of topical cream is about half a centimetre string length. To directly reach the site of inflammation and thus prevent recurrences from posterior areas, vaginal tablets and creams can be applied into the fornix vaginae using applicators. Treatment of the vulva alone, without simultaneous eradication of microorganisms in the vaginal reservoir, may provide temporary symptomatic relief but may not lead to definitive treatment success. The most efficient treatment strategy should not aim to eradicate all fungi from the lower genital tract but to reduce their number so that the patient is asymptomatic. 164

Apart from antimycotics, antiseptic agents, such as dequalinium chloride, can be used as a treatment option. 165 , 166 Octenidine has also been tested as an alternative treatment in cases of acute VVC. 167 , 168 Indeed, there is no need to treat an asymptomatic sexual partner, as this does not offer any benefit for the affected patient. 1 , 169 , 170 It remains unclear whether the treatment of the colonised but asymptomatic partner offers a benefit for the patient.

VVC develops more frequently in HIV-positive women (Table 2). 171 This problem and the multiple issues involved in treatment are examined in appropriate guidelines on the treatment of HIV and opportunistic infections. Sexual partners of HIV-positive women should be informed of the increased risk of infection if they display a predisposition to Candida balanitis. 172 The appropriate statements and recommendations #10-11 are given in Table 1 .

All common vaginal and topical antimycotics are generally well tolerated. Azoles and ciclopiroxolamine may cause slight localised burning in 1-10% of cases. 25 Local reactions or irritations often lead to reduced patient compliance and can be misinterpreted as resistance to therapy. 173 Allergic reactions are still possible but are rare. The hydrophilic fluconazole and lipophilic itraconazole rarely cause side effects at the usual dosages. However, systemic itraconazole causes significantly more side effects than fluconazole, including anaphylactoid reactions and headaches. However, in systemic azole therapy, interactions with other therapeutic agents should also be considered, especially if they are metabolised via cytochrome P450-3A4. When using local azole antifungals, the patient should be informed that the functionality and reliability of rubber diaphragms and latex condoms may be impaired (statement #12, Table 1).

Although vaginal *Candida albicans* species have been found with higher minimal inhibitory concentrations against fluconazole, 174 cases of azole resistance in VVC are rare. 174 , 175 Fluconazole-resistant *Candida* species can be the result of years of indiscriminate drug prescription. Age, previous illnesses, weakened immune system, and severe immunosuppression (e.g., after organ transplantation) are considered risk factors for the development of resistance. Although there is an understanding of azole resistance in yeasts, treatment options for patients with refractory symptoms are limited. New therapeutic options and strategies are needed to address the challenge of azole resistance (recommendation #13, Table 1). 3

The presence of *C. glabrata* often indicates colonisation rather than infection, and typical oral and/or vaginal treatments against *C. glabrata* are usually unsuccessful. In case of *C. glabrata* vaginitis, local administration of nystatin or ciclopiroxolamine might be considered. Sobel et al 176 recommend vaginal application of 600 mg boric acid suppositories for 14 days for *C. glabrata* , while others recommend amphotericin B. 177 The European Chemicals Agency had issued a warning against the application of boric acid, as it can impair fertility and might be embryotoxic. Therefore, boric acid can only be considered as ultima ratio and accompanied by contraceptive measures, when it is being prescribed as a magistral formulation in treatment-resistant cases in non-pregnant women. The use of boric acid should be limited to 'off-label use' in exceptional cases. 8 The magistral formulation with 17% 5-flucytosine was shown to be successful in 90% of the treatment-resistant cases after a two-week vaginal treatment. 176 Treatment with echinocandins (eg micafungin) should be limited to cases with massive complaints as VVC is not approved as treatment indication with little evidence. 178 Vaginitis with *C. krusei* is mostly resistant to fluconazole and itraconazole and partially resistant to posaconazole and some imidazoles. After primary therapy attempt with topical clotrimazole 100 mg for 2 weeks, treatment with ciclopiroxolamine 21 or nystatin might be initiated. 36 Side effects, toxicity, and allergies are not clinically relevant in these treatments, but the available data are limited. Dequalinium chloride is effective in VVC and can be considered, 165 , 166 such as octenidine and other antiseptics that are available. 167 , 168 *C. dubliniensis* appears to have lower virulence compared to *C. albicans* with regard to infections of the deeper tissue and bloodstream. 179 According to currently available data, *C. dubliniensis* is sensitive to imidazole but develops resistance to fluconazole, especially in patients who underwent long-term treatments. 180 *C. tropicalis* and *C. guilliermondii* should be treated similar to *C. albicans*. *C. kefyr* is apathogenic and unlikely to cause vaginitis.

Because infection requires colonisation and disposition, and treatment of underlying disposition (local weakness of the immune system) has not yet been attempted, local and oral maintenance treatments are recommended for the prevention of recurrences. 160 , 181 , 182 , 183 , 184 Chronic recurrent *Candida* vulvovaginitis is comparable to a chronic incurable disease. The results of the treatment with clotrimazole 500 mg locally, ketoconazole 100 mg orally, and fluconazole 150 mg orally are comparable, while ketoconazole is no longer available on the market. The crucial point is

that about half of the patients have relapse shortly after the end of the initial therapy. 160 , 184 In a randomised, placebo-controlled study of 387 women who received 150 mg fluconazole weekly for 6 months, 42.9% of those with fluconazole and 21.9% of those on placebo were disease-free after 12 months. 160 Local nystatin appears to be effective in cases of chronic RVVC, especially in cases of non-*C. albicans* and fluconazole-resistant species. 156

Donders et al 111 , 185 recommend an initial dose of 200 mg fluconazole for 3 days in the first week in cases with chronic RVVC, followed by a maintenance regimen once the patient is free of symptoms or fungi with 200 mg fluconazole once per month for a duration of one year (Figure 1). Almost 90% of patients were disease-free after 6 months treatment, and 77% were disease-free after one year. 111 , 186 The cumulative total dose in the regimen according to Donders is 3,800 mg fluconazole in 6 months and 5,000 mg per year. If 150 mg of fluconazole is administered weekly, the cumulative dose is 3,600 mg at 6 months and 7,200 mg per year, and treatment results are most likely comparable (statements #14-15, Table 1).

Recent evidence suggests that women with familial atopy, prolonged symptom duration, and severe vaginal excoriation have an increased risk of not responding to fluconazole maintenance therapy. 187 However, overall, this therapy is highly effective in the prevention of VVC symptoms, although it is rarely definitively curative. 46 Relapse often occurs again after discontinuation of maintenance therapy. Generally, the development of drug resistance in *C. albicans* isolates after long-term antifungal therapy is a complication about which little is known.

Grinceviciene et al 188 report that sexual behaviour does not appear to be a risk factor for nonresponse to fluconazole maintenance therapy in patients with chronic RVVC. The authors suggest that asymptomatic sexual partners of those with chronic RVVC do not require any treatment to improve recurrence rates. 188 In case the partner develops symptoms or if the yeast is detected on the penis or in the sperm, a single-shot fluconazole 150 mg is indicated for the partner.

Removal of intrauterine pessaries should also be considered in women with chronic RVVC, as *Candida albicans* is more likely to attach to plastic pessaries containing levonorgestrel in women with candidosis than in women without recurrences. 189 After removal of the intrauterine device and treatment with fluconazole, affected women are more likely to stay recurrence-free for a longer time period. 190

In contrast to the treatment of acute VVC, which lasts for 1-7 days, consisting of a typical drug or single-dose treatment and therewith achieving cure rates of > 80%, this is not the case for chronic RVVC. The maintenance therapy with fluconazole reduces the clinical recurrence rate during therapy in patients with RVVC, but there is usually no long-term remission. Moreover, there are well-characterised safety risks for fluconazole, including liver toxicity, drug interactions, and pregnancy warnings.

A potential treatment option in the future might be VT-1161, which is an oral selective inhibitor of fungal lanosterol demethylase (CYP51A1) whose targeted mechanism specifically minimises safety issues and limitations of efficacy. 191 VT-1161 showed strong activity against azole-resistant *C. albicans* and non-*C. albicans* species, such as *C. glabrata* and *C. krusei* , in the treatment of chronic RVVC, with affected patients showing no recurrence for a duration of 48 weeks. 191

Several retrospective studies 190 , 192 , 193 , 194 and one prospective randomised study 195 have reported a significant reduction in preterm birth after vaginal treatment with clotrimazole in cases of VVC during the first trimester of pregnancy. In an Australian study with a relatively small number of cases, a tendency towards reduction of preterm birth after clotrimazole treatment was shown in the first trimester. 196 Another study reported an increased rate of preterm birth after recurrent asymptomatic colonisation with *Candida* in early pregnancy. 197 The negative effect of vaginitis seems to be particularly relevant during the second trimester. 198

Apart from preterm birth, it is well known that the likelihood of term neonates to develop oral thrush or 'diaper dermatitis' during the first year of life is increased in those who are colonised through maternal to neonatal transmission during vaginal delivery. 199 , 200 Therefore, prophylactic antimycotic treatment might be recommended in cases with asymptomatic colonisation during the last weeks of pregnancy to prevent transmission to the newborn during vaginal delivery. This significantly reduces the risk of oral thrush and diaper dermatitis from 10% to 2% in the 4th week of life. 200 , 201 , 202

Oral triazole has widely been used since 1990 and has been considered safe during pregnancy. 192 , 203 The oral intake of 150-300 mg fluconazole has been considered safe during pregnancy, although it was never approved for pregnant women. Indeed, the intake of ≤ 150 mg fluconazole can be considered safe in terms of its embryopathic risk. 13 However, the cumulative dose of 150-6,000 mg fluconazole, administered during the first trimester, has been associated with a significantly increased risk of foetal tetralogy of Fallot, according to a large Danish registry study (odds ratio 3.16, 95% confidence interval 1.49-6.71). 204

The same research group also reported an increased risk of miscarriage after oral fluconazole intake during early pregnancy. 205 The US National Birth Defects Prevention Study analysed data from 43,257 women and found a significant association between low-dose fluconazole use during the first trimester and incidence of foetal cleft lip and palate and transposition of the large vessels. 206 Although there are few clinical studies on the use of dequalinium chloride as an alternative treatment during pregnancy, available data suggest good tolerability and effectiveness. 165 , 166 , 168 Therefore, dequalinium chloride might be a therapeutic option for VVC during pregnancy. The appropriate recommendation #16 is given in Table 1 .

Nowadays, self-medication or over-the-counter therapy of VVC with clotrimazole and, in some countries, with fluconazole is practised in 80% of cases. Hopeful expectations in the early 1990s that were based on reports of patients that almost always correctly diagnosed themselves with VVC has been proven incorrect. 71 , 207 However, it seems that only one-third of women who have practised antifungal self-medication actually had VVC. 208 This suggests that treatment should only be administered after a correct, medically confirmed diagnosis to avoid further resistance and unjustified side effects of the treatment (recommendation #17, Table 1).

Due to the antagonistic effect of some lactobacilli in *Candida* -induced vulvovaginitis, probiotics are considered a natural approach for the prevention and treatment of vaginal infections. Extragenital sites, such as the intestine, serve as a reservoir for recolonisation in women with chronic RVVC, 209 so that oral probiotics may also be considered in women with chronic RVVC and those with a contraindication to antifungal therapy. 8 , 210

In addition to the oral administration of probiotics, the intramuscular injection of non-H₂O₂-forming lactobacilli, which leads to nonspecific immune stimulation and formation of antibodies, has shown encouraging results. 211 , 212 , 213 , 214 Lactobacilli have been identified to have a direct antifungal or immunostimulatory effect in vitro. 97 They also seem to significantly reduce fungal colonisation in vivo after VVC therapy. 98 One study showed that the monthly addition of lactobacilli for 6 days in addition to a single dose of itraconazole did not improve the recurrence rate of RVVC compared to itraconazole alone. However, the probiotics were more effective than homeopathy. 215 In another study on vaginal *L. plantarum* I1001, the treatment increased the effectiveness of a single dose of 500 mg clotrimazole in the prevention of VVC recurrence. 216

The strategy of recurrence prevention might also be attributable to *C. glabrata* vaginitis. 217 Probiotics can block the passage of pathogenic microbes from the gastrointestinal tract to the vagina, modulate the host's immune response, and influence the epithelial defences and thus the expression of inflammatory genes induced by VVC. Apart from that, probiotics have a direct fungicidal effect, which can inhibit the growth of *Candida* and impede its adhesion to epithelial cells. 218 In addition to lactobacilli, lactoferrin, which is an iron-binding glycoprotein that can be found in milk and cervical mucus, is an interesting compound to reduce the risk of vaginal candidosis. Russo

et al 210 examined the ability of an oral mixture of lactobacilli with lactoferrin to reduce the recurrence of VVC clotrimazole treatment, and the results were promising (statement #18, Table 1).

Boric acid is known for its antibacterial, antifungal, and antiviral activity and its antiseptic and astringent characteristic. Used as a topical powder, boric acid can potentially help control fungal growth, relieve itching and inflammation, and accelerate the healing process. Sobel et al 219 reported that in 73 patients with symptomatic vaginitis who were treated with boric acid, 64% had fewer symptoms followed by negative culture result. Sobel and Chaim also found that boric acid led to a mycological eradication rate of 77%, with final healing in 81% of the cases. 220 Boric acid capsules can be prescribed as a magistral formulation. However, they should not be used as first-line treatment. 8 In contrast, the use of boric acid should be limited to 'off-label use' for exceptional cases.

Another alternative for the treatment of resistant cases is iodine of povidone (PVP-I) or iodopovidone, a chemical complex that contains 9-12% active iodine. PVP-I has a broad spectrum of germicidal effects against gram-positive and gram-negative bacteria, viruses, and fungi. It is used as an antiseptic topical solution, ointment, or vaginal suppository. The mechanisms of PVP-I are based on the oxidation of amino acids. An antifungal effect and effect against *Trichomonas vaginalis* have been proven for PVP-I in vitro, as it inhibits the formation of biofilms. Moreover, it has also shown to provide rapid relief of symptoms. 8

Propolis has been described as a promising alternative in the treatment of VVC. The effects of propolis are antimicrobial, anti-inflammatory, antiseptic, hepatoprotective, antitumoural, immunomodulatory, wound healing, anaesthetic, and antioxidant. Capoci et al 8 , 221 reported an antifungal effect of propolis on *C. albicans* and its inhibition of biofilm formation as a possible preventive strategy in cases of VVC. Dermatologists have also known propolis for its ability to trigger contact allergies. 7 The antifungal effect of the plant *Salvia officinalis* is attributed to the presence of *cis*-thujone and camphor. Treatment with *salvia* vaginal tablets, with or without clotrimazole, was shown to be effective against *C. albicans* . 222

Finally, progesterone might be a treatment option in case of chronic RVVC. 109 , 223 One study evaluated long-term administration of the ovulation inhibitor medroxyprogesterone acetate (MPA) for the treatment of chronic RVVC, including evaluation of relapse, side effects, and consumption of antimycotics in 20 women using a visual analogue scale. MPA, as well as the use of antifungals in the second year of use, was shown to reduce symptoms. 109 However, intrauterine devices might in turn increase the susceptibility of infections due to fungal adhesion (recommendation #19, Table 1). 77

More than 30 years ago, Rosedale and Brown presented their encouraging results on hypersensitisation in candidosis. 224 In vitro studies with an autologous membrane-bound *C. albicans* antigen from a patient with chronic RVVC showed improved immunological responses compared to commercially available *Candida* antigens. 225 , 226 However, to date, there are no approved immunotherapeutic agents or vaccines available against fungal infections. 44 A safe and effective vaccine would significantly improve the management of chronic RVVC. The vaccines NDV-3A (clinical phases 1 and 2 completed) 227 and PEV-7 are potential candidates that might be available in the near future. 228 Rigg et al, 229 Moraes et al, 230 and Rusch and Schwartz 231 reported promising results for allergen immunotherapies, but despite these efforts, there is no therapeutic breakthrough so far. 22 , 237

In addition to the approach to induce antibody formation against systemic candidosis, vaccines against oral thrush and VVC have entered initial clinical trials. In animal models and early-phase trials, these vaccines have shown good antibody formation. 114 , 118 In a preclinical study, the vaccine candidate NDV-3 was tested, which contains the N-terminal part of the *C. albicans* agglutinin-like sequence 3 protein (Als3p), formulated with an aluminium hydroxide adjuvant in phosphate-buffered salt solution. In an animal model, Als3p has been shown to protect from

oropharyngeal, vaginal, and disseminated candidosis and from skin and soft tissue infections with *Staphylococcus aureus*. 238, 239 Another study showed that a single administration of live *Saccharomyces cerevisiae* cells induces *Candida* clearance in amounts that were comparable to fluconazole treatment. 240

The intramuscular injection of non-H₂O₂-forming 'aberrant' lactobacilli has also demonstrated the ability to induce antibody formation and unspecific immune response, showing promising results for VVC, trichomoniasis, and bacterial vaginosis. Although the injection does not reduce the number of relapses in cases of chronic RVVC, it leads to a significant improvement in physical and mental performance (statement #20, table 1). 246

A number of gaps remain in our knowledge of *Candida*–host interactions, and these gaps require further research. In addition to VT1161, which was previously mentioned, the beta-glucan synthase inhibitor Ibrexafungerp (formerly SCY078) is a promising candidate, 191 particularly in patients with chronic RVVC who have not responded adequately to fluconazole maintenance therapy. 72, 241, 242, 243 There are also new formulations that exist for vaginal application, including the combination of clotrimazole with the non-steroidal analgesic diclofenac (Prof001, phase 3). Provided that the results of the phase 3 studies continue to be as promising as before, the market entry of new active substances could significantly improve the treatment of chronic RVVC in particular. Nevertheless, the remaining gaps in knowledge that require further research include the following: How can virulence factors of *C. albicans* be combated? How can the adhesion of *Candida* cells to the vaginal epithelium be inhibited? How can the resistance of the vagina (T lymphocyte stimulation, humoral factors, allergy) be improved? What are the interactions of *Candida* with the vaginal flora? Can we prove in vitro and in vivo that apathogenic edible yeasts also cause mycosis? This leads us to the following important clinical questions that need to be answered in the future: What should we do about the increase in resistance? What alternative therapies exist in cases of fluconazole resistance? Are oral probiotics equivalent to common antifungals or is their use limited to act as a supportive agent for the prevention of chronic RVVC? Some questions remain to be elucidated, and this underlines the fact that this field remains interesting and open for future preclinical, translational, and clinical research (recommendation #21, Table 1).

Conflicts of interest statements of the authors are given in the German full-text version: <https://www.awmf.org/leitlinien/detail/II/015072.html>.

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