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REVIEW ARTICLE

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

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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-*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.

KEYWORDS
Candida, candidosis, diagnosis, therapy, vulvovaginal candidosis

1 | INTRODUCTION

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-*albicans* species, such as *C glabrata*, *C tropicalis*, *C krusei* and *C parapsilosis*.[8] Infections with non-*albicans* species are often accompanied by milder symptoms than those in vaginitis caused by *C albicans*. Non-*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-*albicans* species are often non-responsive 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.

2 | MATERIALS AND METHODS

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[2,9-14] and four published guidelines were found,[15-18] 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.

3 | DEFINITION

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.

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 2-4), 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]

Non-*albicans* species, particularly *C glabrata*, are more commonly observed in postmenopausal, diabetic and immunocompromised women.[28-33] *C krusei*, *C guilliermondii*, *C tropicalis*, *C parapsilosis* and others can cause vulvovaginitis with typical symptoms,[1,34-36] 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]

TABLE 1 Consensus-based recommendations and statements

No.	Strength	Recommendation *or* statement
#1	++	The terms 'candidosis' and '*Candida* vulvovaginitis' should be preferred over the term 'candidiasis'
#2	+++	In premenopausal, pregnant, asymptomatic, healthy women, as well as women with acute VVC (without a history of chronic recurrent vulvovaginal candidosis), the predominant species is *Candida albicans*
#3	+++	The step from colonisation to vaginitis is not yet fully understood and demonstrates the importance of host factors
#4	+++	The colonisation with *Candida* species is frequent, often temporary and does usually not require any treatment, if the affected woman is not pregnant
#5	+++	About 70-75% of all women suffer at least once in their life from vulvovaginal candidosis, and there are certain risk groups, which should not only undergo proper diagnosis and treatment, but also (if possible) elimination of predisposing host factors
#6	+++	Itching is the predominant symptom of vulvovaginal candidosis, but not all women who report itching suffer from vulvovaginal candidosis. In addition to itching, affected women often complain of vaginal redness, a feeling of soreness, burning, dyspareunia and dysuria. Symptoms are not unsuitable to differentiate between the different causes of vaginitis
#7	+++	The diagnostic procedure to detect vulvovaginal candidosis should involve the combination of clinical features and the microscopic detection of (pseudo-)hyphae and be expanded to cultural methods in unclear cases
#8	+++	Microscopic examination of vaginal using light or phase contrast microscopy with 400 × optical magnification should be carried out as the first diagnostic step
#9	+++	Serological tests, especially antibody level determinations, are not necessary for diagnosing vulvovaginal candidosis
#10	+++	Acute vulvovaginal candidosis should be treated with local or oral antimycotics (depending on the individual needs of the woman), while chronic recurrent vulvovaginal candidosis should be treated orally and potentially involve dose-reducing suppression regimens
#11	+++	Treatment of acute vulvovaginal candidosis with topical or oral imidazole derivatives, polyenes and ciclopiroxolamine shows equivalent success. There is no need to treat an asymptomatic sexual partner in cases with acute vulvovaginal candidosis
#12	+++	All commonly available vaginal and topical antimycotics are generally well tolerated
#13	+++	Unnecessary antifungal therapies can lead to resistance by selecting less-sensitive species and should therefore be avoided
#14	+++	In women with chronic recurrent vulvovaginal candidosis or non-*albicans* vaginitis, it should be reevaluated whether the symptoms indicate mycosis, and whether second-line treatments are used following resistance testing. This applies to for example *Candida glabrata*
#15	+++	Long-term antifungal treatments can be used for chronic recurrent vulvovaginal candidosis, using various regimens with little evidence
#16	+++	Treatment for vulvovaginal candidosis during pregnancy should involve local clotrimazole, especially during the first trimester, in order to avoid foetal malformations and miscarriage
#17	+++	Treatment for vulvovaginal candidosis should always follow proper diagnostic work-up, based on medical anamnesis, symptoms, microscopy and, in some cases, cultural methods
#18	+++	Probiotics appear to be beneficial in the prevention of vulvovaginal candidosis, but the evidence is limited
#19	+++	There are various alternative and complementary treatment strategies for vulvovaginal candidosis, but these treatment strategies are rarely evidence-based
#20	+++	There are no approved immunotherapies against vulvovaginal candidosis available
#21	+++	There is need for preclinical, translational and clinical research in the field of vulvovaginal candidosis and chronic recurrent vulvovaginal candidosis

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

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]

5 | HOST FACTORS

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

TABLE 2 *Candida* colonisation of the vagina in HIV-positive or HIV-negative women[129]

	HIV-positive (24/66 36.4%)		HIV-negative (88/383, 22.9%)		
***Candida* species**	**N**	**%**	**N**	**%**	***p***
C albicans	14	58.3	77	87.5	
C glabrata	8	33.3	6	6.8	
C krusei	0	-	2	2.3	
C dubliniensis	0	-	1	1.1	**.001**
C parapsilosis	1	4.2	1	1.1	
C famata	0	-	1	1.1	
C magnoliae	1	4.2	0	-	
Total	24	100	88	100	.02

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.[47-49] 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[50-52] 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.[61-63]

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 Schwebke 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.

6 | GENITAL COLONISATION

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).

TABLE 3 *Candida* species in patients with positive vaginal culture[129]

***Candida* species**	**Premenopausal (82/338, 24.3%)**		**Postmenopausal (6/45, 13.3%)**		**Pregnant (52/192, 27.1%)**		**Non-pregnant (30/146, 20.5%)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	***P* =.003**				***P* =.02**			
C albicans	75	91.5	2	33.3	48	92.4	27	90
C glabrata	4	4.9	2	33.3	2	3.8	2	6.7
C krusei	1	1.2	1	16.7	1	1.9	0	-
C dubliniensis	1	1.2	0	-	1	1.9	0	-
C famata	0	-	1	16.7	0	-	0	-
C parapsilosis	1	1.2	-	-	0	-	1	3.3
Total	82	100	6	100	52	100	30	100

TABLE 4 Distribution of *Candida* species in women with acute VVC in Europe[25]

Candida species	n	%
C albicans	450	94.8
C glabrata	10	2.1
C krusei	4	0.8
Others (*C tropicalis*, *C kefyr*, *C africana*, *S cerevisiae*)	11	2.3
Total	475	100

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]

7 | PREDISPOSING FACTORS

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).

7.1 | Diabetes mellitus

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.[43-46,78,79] 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]

7.2 | Antibiotic use

Women who already have *Candida* colonisation have an increased risk of developing VVC after antibiotic treatment.[87-90] 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]

7.3 | Vaginal microbiota

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*.[96-100] 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]

7.4 | Hormonal factors

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.[43-45] 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]

7.5 | Contraceptive use

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.

7.6 | Genetic factors

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 AB0 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. Th-1-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.[114-118] 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]

7.7 | Lifestyle factors

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.

8 | SYMPTOMS

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.[26,134-137] 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]

9 | DIAGNOSIS

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 unneccessary.[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™ 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-*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.

10 | TREATMENT

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).

10.1 | Acute vaginitis

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.[9,25,159-161] 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]

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.

10.2 | Possible side-effects

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

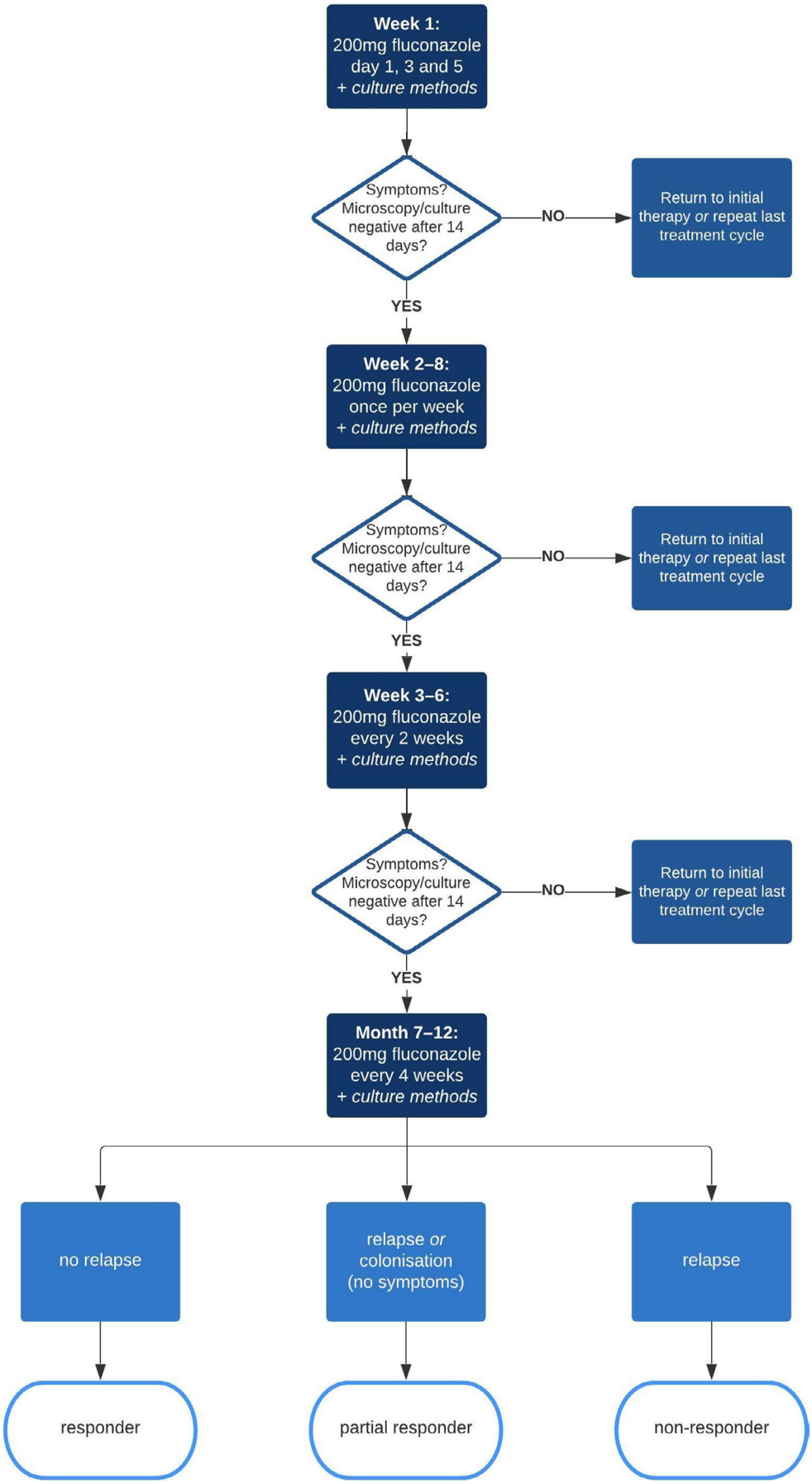

FIGURE 1 Maintenance therapy with fluconazole in patients with chronic RVVC

TABLE 5 Treatment options for patients with acute VVC

Local treatment (mild to normal symptoms)		
Clotrimazole	200 mg vaginal tablets, once daily (3 days)	
	500 mg vaginal tablet, once daily (1 day)	
Econazole	150 mg vaginal suppository, twice daily (1 day)	
	150 mg vaginal suppository, once daily (3 days)	
Fenticonazole	600 mg vaginal capsule, once daily (1 day)	*repeat in case of relapse*
Isoconazole	150 mg vaginal suppository, twice daily (1 day)	
	150 mg vaginal suppository, once daily (3 days)	
	600 mg vaginal suppository, once daily (1 day)	
Alternative treatment (severe symptoms)		
Fluconazole	150 mg orally, single shot	
	50 mg orally, once daily (7-14 days)	
	100 mg orally, once daily (14 days)	*for immunocompromised patients*
Itraconazole	100 mg orally 2 × 2 capsules daily (1 day)	
	100 mg orally 1 × 2 capsules daily (3 days)	
Nystatin	100.000 units vaginal tablets (14 days)	
	200.000 units vaginal tablets (6 days)	
Ciclopiroxolamine	50 mg (applicator), once daily (6-14 days)	*through international pharmacy*

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).

10.3 | Treatment resistance

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]

10.4 | Non-*albicans* vaginitis

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 teratments.[180] *C tropicalis* and *C guilliermondii* should be treated similar to *C albicans*. *C kefyr* is apathogenic and unlikely to cause vaginitis.

10.5 | Chronic recurrent *Candida* vulvovaginitis

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.[160,181-184] 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-*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-*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]

10.6 | Treatment during pregnancy

Several retrospective studies[190,192-194] 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.[200-202]

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.

10.7 | Self-medication

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).

10.8 | Probiotic use

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-H_2O_2-forming lactobacilli, which leads to nonspecific immune stimulation and formation of antibodies, has shown encouraging results.[211-214] 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).

10.9 | Alternative and complementary strategies

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]

11 | FUTURE PERSPECTIVES

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 Schwiertz[231] reported promising results for allergen immunotherapies, but despite these efforts, there is no therapeutic breakthrough so far.[22,42,50,120,121,233-237]

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-H_2O_2-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]

12 | FUTURE RESEARCH

A number of gaps remain in our knowledge of *Candida*–host interactions, and these gaps require further research. In addition to VT-1161, which was previously mentioned, the beta-glucan synthase inhibitor Ibrexafungerp (formerly SCY-078) is a promising candidate,[191] particularly in patients with chronic RVVC who have not responded adequately to fluconazole maintenance therapy.[72,241-243] There are also new formulations that exist for vaginal application, including the combination of clotrimazole with the non-steroidal analgesic diclofenac (ProF-001, 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).

CONFLICT OF INTEREST STATEMENT

Conflicts of interest statements of the authors are given in the German full-text version: https://www.awmf.org/leitlinien/detail/ll/015-072.html.

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REFERENCES

1. Sobel JD. Vulvovaginal candidosis. *Lancet*. 2007;369(9577):1961-1971.
2. Xie HY, Feng D, Wei DM, et al. Probiotics for vulvovaginal candidiasis in non-pregnant women. *Cochrane Database Syst Rev*. 2017;11:CD010496.
3. Barajas JF, Wehrs M, To M, et al. Isolation and characterization of bacterial cellulase Producers for biomass deconstruction. A microbiology laboratory course. *J Microbiol Biol Educ*. 2019;20(2).
4. Cole AM. Innate host defense of human vaginal and cervical mucosae. *Curr Top Microbiol Immunol*. 2006;306:199-230.
5. Denning DW, Kneale M, Sobel JD, Rautemaa-Richardson R. Global burden of recurrent vulvovaginal candidiasis: a systematic review. *Lancet Infect Dis*. 2018;18(11):e339-e347.
6. Yano J, Sobel JD, Nyirjesy P, et al. Current patient perspectives of vulvovaginal candidiasis: incidence, symptoms, management and post-treatment outcomes. *BMC Womens Health*. 2019;19(1):48.
7. Nyman GSA, Tang M, Inerot A, Osmancevic A, Malmberg P, Hagvall L. Contact allergy to beeswax and propolis among patients with cheilitis or facial dermatitis. *Contact Dermatitis*. 2019;81(2):110-116.
8. Thais Chimati Felix DvDdBR, Reginaldo dos Santos Pedroso. Alternative and complementary therapies for vulvovaginal candidiasis. *Folia Microbiol*. 2019;2018(64):133-141.
9. Pitsouni E, Iavazzo C, Falagas ME. Itraconazole vs fluconazole for the treatment of uncomplicated acute vaginal and vulvovaginal candidiasis in nonpregnant women: a metaanalysis of randomized controlled trials. *Am J Obstet Gynecol*. 2008;198(2):153-160.
10. Roberts CL, Algert CS, Rickard KL, Morris JM. Treatment of vaginal candidiasis for the prevention of preterm birth: a systematic review and meta-analysis. *Syst Rev*. 2015;4:31.
11. Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal agents for the treatment of uncomplicated vulvovaginal candidiasis (thrush): a systematic review. *BJOG*. 2002;109:85-95.
12. Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy. *Cochrane Database Syst Rev*. 2001;4. https://doi.org/10.1002/14651858.CD000225
13. Howley MM. Using meta-analyses to improve risk estimates of specific birth defects. *BJOG*. 2019;126(13):1553.
14. Hanson L, VandeVusse L, Jerme M, Abad CL, Safdar N. Probiotics for treatment and prevention of urogenital Infections in women: A systematic review. *J Midwifery Womens Health*. 2016;61(3):339-355.
15. Die Vulvovaginalkandidose WM. 2010.
16. Mendling W, Brasch J. Guideline vulvovaginal candidosis (2010) of the German Society for Gynecology and Obstetrics, the Working Group for Infections and Infectimmunology in Gynecology and Obstetrics, the German Society of Dermatology, the Board of German Dermatologists and the German Speaking Mycological Society. *Mycoses*. 2012;55(Suppl 3):1-13.
17. Mendling W, Brasch J, Cornely OA, et al. Guideline: vulvovaginal candidosis (AWMF 015/072), S2k (excluding chronic mucocutaneous candidosis). *Mycoses*. 2015;58(Suppl 1):1-15.
18. Bond CM, Watson MC. Grampian evidence based community pharmacy guidelines G. The development of evidence-based guidelines for over-the-counter treatment of vulvovaginal candidiasis. *Pharm World Sci*. 2003;25(4):177-181.
19. Odds FC, Arai T, Disalvo AF, et al. Nomenclature of fungal diseases: a report and recommendations from a Sub-Committee of the International Society for Human and Animal Mycology (ISHAM). *J Med Veterin Mycol*. 1992;30(1):1-10.
20. Loeffler W. Terminology of human mycoses. Nomenclature of mycotic diseases of man. List of accepted German terms translated, arranged and published, together with comments, for the International Society for Human and Animal Mycology (ISHAM). *Mykosen*. 1983;26(7):346-384.
21. Vaginose WM. Vaginitis, Zervizitis und Salpingitis. 2006.
22. De Bernardis F, Boccanera M, Cassone A. The role of humoral immunity against vaginal candida infection. *Fungal Immunology. Springer*. 2005;345-355.
23. Romeo O, Criseo G. Candida africana and its closest relatives. *Mycoses*. 2011;54(6):475-486.
24. Sharma C, Muralidhar S, Xu J, Meis JF, Chowdhary A. Multilocus sequence typing of *Candida africana* from patients with vulvovaginal candidiasis in New Delhi. *India. Mycoses*. 2014;57(9):544-552.
25. Mendling W, Krauss C, Fladung B. A clinical multicenter study comparing efficacy and tolerability of topical combination therapy with clotrimazole (Canesten, two formats) with oral single dose fluconazole (Diflucan) in vulvovaginal mycoses. *Mycoses*. 2004;47(3–4):136-142.
26. Hettiarachchi N, Ashbee HR, Wilson JD. Prevalence and management of non-albicans vaginal candidiasis. *Sex Transm Infect*. 2010;86(2):99-100.
27. Vermitsky J-P, Self MJ, Chadwick SG, et al. Survey of vaginal-flora Candida species isolates from women of different age groups by use of species-specific PCR detection. *J Clin Microbiol*. 2008;46(4):1501-1503.
28. Goswami R, Dadhwal V, Tejaswi S, et al. Species-specific prevalence of vaginal candidiasis among patients with

diabetes mellitus and its relation to their glycaemic status. *J Infect*. 2000;41(2):162-166.
29. Goswami D, Goswami R, Banerjee U, et al. Pattern of Candida species isolated from patients with diabetes mellitus and vulvovaginal candidiasis and their response to single dose oral fluconazole therapy. *J Infect*. 2006;52(2):111-117.
30. de Leon EM, Jacober SJ, Sobel JD, Foxman B. Prevalence and risk factors for vaginal Candida colonization in women with type 1 and type 2 diabetes. *BMC Infect Dis*. 2002;2:1.
31. Corsello S, Spinillo A, Osnengo G, et al. An epidemiological survey of vulvovaginal candidiasis in Italy. *Eur J Obstet Gynecol Reprod Biol*. 2003;110(1):66-72.
32. Paulitsch A, Weger W, Ginter-Hanselmayer G, Marth E, Buzina W. A 5-year (2000–2004) epidemiological survey of Candida and non-Candida yeast species causing vulvovaginal candidiasis in Graz. *Austria. Mycoses*. 2006;49(6):471-475.
33. [33]Odds F. *Candida and Candidosis*, 2nd edn. London: Bailliere Tindall (WB Saunders); 1988.
34. Nyirjesy P, Alexander AB, Weitz MV. Vaginal Candida parapsilosis: pathogen or bystander? *Infect Dis Obstet Gynecol*. 2005;13(1):37-41.
35. Spinillo A, Capuzzo E, Nicola S, Baltaro F, Ferrari A, Monaco A. The impact of oral contraception on vulvovaginal candidiasis. *Contraception*. 1995;51(5):293-297.
36. Singh S, Sobel JD, Bhargava P, Boikov D, Vazquez JA. Vaginitis due to Candida krusei: epidemiology, clinical aspects, and therapy. *Clin Infect Dis*. 2002;35(9):1066-1070.
37. Sobel JD, Vazquez J, Lynch M, Meriwether C, Zervos MJ. Vaginitis due to Saccharomyces cerevisiae: epidemiology, clinical aspects, and therapy. *Clin Infect Dis*. 1993;16(1):93-99.
38. Li J, Fan SR, Liu XP, et al. Biased genotype distributions of Candida albicans strains associated with vulvovaginal candidosis and candidal balanoposthitis in China. *Clin Infect Dis*. 2008;47(9):1119-1125.
39. Mendling WGJ, Gantenberg R. Vergleich der Stammspezifität von Hefepilzen verschiedener Lokalisation bei Frauen mit Vaginalcandidiosen.*Mycoses*. 1998;41:23-25.
40. Odds FC, Bernaerts R. CHROMagar Candida, a new differential isolation medium for presumptive identification of clinically important Candida species. *J Clin Microbiol*. 1994;32(8):1923-1929.
41. Sullivan DJ, Moran GP, Coleman DC. Candida dubliniensis: ten years on. *FEMS Microbiol Lett*. 2005;253(1):9-17.
42. Fidel PL Jr. Immunity in vaginal candidiasis. *Curr Opin Infect Dis*. 2005;18(2):107-111.
43. Yano J, Peters BM, Noverr MC, Fidel PL Jr. Novel mechanism behind the immunopathogenesis of vulvovaginal candidiasis: "Neutrophil Anergy". *Infect Immun*. 2018;86(3):e00684-17. https://doi.org/10.1128/IAI.00684-17
44. Willems HME, Ahmed SS, Liu J, Xu Z, Peters BM. Vulvovaginal candidiasis: a current understanding and burning questions. *J Fungi (Basel)*. 2020;6(1):27. https://doi.org/10.3390/jof6010027
45. Naglik JR, Gaffen SL, Hube B. Candidalysin: discovery and function in *Candida albicans* infections. *Curr Opin Microbiol*. 2019;52:100-109.
46. Ho J, Wickramasinghe DN, Nikou SA, Hube B, Richardson JP, Naglik JR. Candidalysin is a potent trigger of alarmin and antimicrobial peptide release in epithelial cells. *Cells*. 2020;9(3):699. https://doi.org/10.3390/cells9030699
47. Farrell SM, Hawkins DF, Ryder TA. Scanning electron microscope study of *Candida albicans* invasion of cultured human cervical epithelial cells. *Sabouraudia*. 1983;21(3):251-254.
48. David J, Trumbore JS. Recurrent vuvovaginal Candidiasis: vaginal epithelial cell susceptibility to *Candida albicans* adherence.*Obstet Gynecol*. 1986;67(6):810-812.
49. Sobel JD, Myers PG, Kaye D, Levison ME. Adherence of Candida albicans to human vaginal and buccal epithelial cells. *J Infect Dis*. 1981;143(1):76-82.
50. De Bernardis F, Agatensi L, Ross IK, et al. Evidence for a role for secreted aspartate proteinase of Candida albicans in vulvovaginal candidiasis. *J Infect Dis*. 1990;161(6):1276-1283.
51. Naglik J, Albrecht A, Bader O, Hube B. Candida albicans proteinases and host/pathogen interactions. *Cell Microbiol*. 2004;6(10):915-926.
52. Ruchel R, Tegeler R, Trost M. A comparison of secretory proteinases from different strains of *Candida albicans*. *Sabouraudia*. 1982;20(3):233-244.
53. Ghannoum MA. Potential role of phospholipases in virulence and fungal pathogenesis. *Clin Microbiol Rev*. 2000;13(1):122-143, table of contents.
54. Cassone A, De Bernardis F, Mondello F, Ceddia T, Agatensi L. Evidence for a correlation between proteinase secretion and vulvovaginal candidosis. *J Infect Dis*. 1987;156(5):777-783.
55. Ghannoum MA, Abu-Elteen KH. Pathogenicity determinants of Candida. *Mycoses*. 1990;33(6):265-282.
56. Ismail A, Lupan DM. Utilization of siderophores by *Candida albicans*. *Mycopathologia*. 1986;96(2):109-113.
57. Meinhof W. Hydrochloric acid tolerance of *Candida albicans*. *Mykosen*. 1974;17(12):339-347.
58. Lattif AA, Prasad R, Banerjee U, Gupta N, Mohammad S, Baquer NZ. The glyoxylate cycle enzyme activities in the pathogenic isolates of *Candida albicans* obtained from HIV/AIDS, diabetic and burn patients. *Mycoses*. 2006;49(2):85-90.
59. Roselletti E, Monari C, Sabbatini S, et al. A role for yeast/pseudohyphal cells of *Candida albicans* in the correlated expression of NLRP3 Inflammasome inducers in women with acute vulvovaginal candidiasis. *Front Microbiol*. 2019;10:2669.
60. Cunha C, Carvalho A, Esposito A, Bistoni F, Romani L. DAMP signaling in fungal infections and diseases. *Front Immunol*. 2012;3:286.
61. Roselletti E, Perito S, Gabrielli E, et al. NLRP3 inflammasome is a key player in human vulvovaginal disease caused by Candida albicans. *Sci Rep*. 2017;7(1):17877.
62. Pericolini E, Perito S, Castagnoli A, et al. Epitope unmasking in vulvovaginal candidiasis is associated with hyphal growth and neutrophilic infiltration. *PLoS One*. 2018;13(7):e0201436.
63. Camilli G, Tabouret G, Quintin J. The complexity of fungal beta-glucan in health and disease: effects on the mononuclear phagocyte system. *Front Immunol*. 2018;9:673.
64. Muzny CA, Schwebke JR. Biofilms: an underappreciated mechanism of treatment failure and recurrence in vaginal infections. *Clin Infect Dis*. 2015;61(4):601-606.
65. Auler ME, Morreira D, Rodrigues FFO, et al. Biofilm formation on intrauterine devices in patients with recurrent vulvovaginal candidiasis. *Med Mycol*. 2010;48(1):211-216.
66. Chassot F, Negri MFN, Svidzinski AE, et al. Can intrauterine contraceptive devices be a Candida albicans reservoir? *Contraception*. 2008;77(5):355-359.
67. Zhao X, Malloy PJ, Ardies CM, Feldman D. Oestrogen-binding protein in Candida albicans: antibody development and cellular localization by electron immunocytochemistry. *Microbiology*. 1995;141(Pt 10):2685-2692.
68. Dennerstein GJ, Ellis DH. Oestrogen, glcogen and vaginal candidiasis. *Obstet Gynecol*. 2001;41:326.
69. Dennerstein GJ, Ellis DH. Oestrogen, glycogen and vaginal candidiasis. *Aust N Z J Obstet Gynaecol*. 2001;41(3):326-328.
70. Weissenbacher T, Witkin SS, Ledger WJ, et al. Relationship between clinical diagnosis of recurrent vulvovaginal candidiasis and detection of Candida species by culture and polymerase chain reaction. *Arch Gynecol Obstet*. 2009;279(2):125-129.

71. Beigi RH, Meyn LA, Moore DM, Krohn MA, Hillier SL. Vaginal yeast colonization in nonpregnant women: a longitudinal study. *Obstet Gynecol*. 2004;104(5 Pt 1):926-930.
72. Ruhnke M, Grosch-Worner I, Lischewski A, et al. Genotypic relatedness of yeast isolates from women infected with human immunodeficiency virus and their children. *Mycoses*. 1999;42(5–6):385-394.
73. Tapia CV, Hermosilla G, Fortes P, et al. Genotyping and persistence of *Candida albicans* from pregnant women with vulvovaginal candidiasis. *Mycopathologia*. 2017;182(3–4):339-347.
74. Foxman B, Muraglia R, Dietz JP, Sobel JD, Wagner J. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. *J Low Genit Tract Dis*. 2013;17(3):340-345.
75. Bohannon NJ. Treatment of vulvovaginal candidiasis in patients with diabetes. *Diabetes Care*. 1998;21(3):451-456.
76. Marschalek J, Farr A, Kiss H, et al. Risk of vaginal infections at early gestation in patients with diabetic conditions during pregnancy: a retrospective cohort study. *PLoS One*. 2016;11(5):e0155182.
77. Donders GGG, Bellen G, Ruban K, Van Bulck B. Short- and long-term influence of the levonorgestrel-releasing intrauterine system (Mirena(R)) on vaginal microbiota and Candida. *J Med Microbiol*. 2018;67(3):308-313.
78. Ahmed MO, Elramalli AK, Baptiste KE, et al. Whole genome sequence analysis of the first vancomycin-resistant *Enterococcus faecium* Isolates from a Libyan Hospital in Tripoli. *Microb Drug Resist*. 2020;26(11):1390-1398.
79. Houston DK, Neiberg RH, Miller ME, et al. Physical function following a long-term lifestyle intervention among middle aged and older adults with type 2 diabetes: the look AHEAD study. *J Gerontol A Biol Sci Med Sci*. 2018;73(11):1552-1559.
80. Zhang X, Liao Q, Wang F, Li D. Association of gestational diabetes mellitus and abnormal vaginal flora with adverse pregnancy outcomes. *Medicine (Baltimore)*. 2018;97(34):e11891.
81. Donders GG, Prenen H, Verbeke G, Reybrouck R. Impaired tolerance for glucose in women with recurrent vaginal candidiasis. *Am J Obstet Gynecol*. 2002;187(4):989-993.
82. Ray D, Goswami R, Banerjee U, et al. Prevalence of Candida glabrata and its response to boric acid vaginal suppositories in comparison with oral fluconazole in patients with diabetes and vulvovaginal candidiasis. *Diabetes Care*. 2007;30(2):312-317.
83. Unnikrishnan AG, Kalra S, Purandare V, Vasnawala H. Genital infections with sodium glucose cotransporter-2 inhibitors: occurrence and management in patients with type 2 diabetes mellitus. *Indian J Endocrinol Metab*. 2018;22(6):837-842.
84. Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *Curr Med Res Opin*. 2014;30(6):1109-1119.
85. Sawyer SM, Bowes G, Phelan PD. Vulvovaginal candidiasis in young women with cystic fibrosis. *BMJ*. 1994;308(6944):1609.
86. Sawyer SM, Phelan PD, Bowes G. Reproductive health in young women with cystic fibrosis: knowledge, behavior and attitudes. *J Adolesc Health*. 1995;17(1):46-50.
87. Pirotta MV, Gunn JM, Chondros P. "Not thrush again!" Women's experience of post-antibiotic vulvovaginitis. *Med J Aust*. 2003;179(1):43-46.
88. Pirotta MV, Garland SM. Genital Candida species detected in samples from women in Melbourne, Australia, before and after treatment with antibiotics. *J Clin Microbiol*. 2006;44(9):3213-3217.
89. Xu J, Schwartz K, Bartoces M, Monsur J, Severson RK, Sobel JD. Effect of antibiotics on vulvovaginal candidiasis: a MetroNet study. *J Am Board Fam Med*. 2008;21(4):261-268.
90. Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes KK. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. *Obstet Gynecol*. 1998;92(5):757-765.
91. Shukla A, Sobel JD. Vulvovaginitis caused by *Candida* species following antibiotic exposure. *Curr Infect Dis Rep*. 2019;21(11):44.
92. Auger P, Joly J. Microbial flora associated with *Candida albicans* vulvovaginitis. *Obstet Gynecol*. 1980;55(3):397-401.
93. Swidsinski A, Loening-Baucke V, Mendling W, et al. Infection through structured polymicrobial Gardnerella biofilms (StPM-GB). *Histol Histopathol*. 2014;29(5):567-587.
94. Hummelen R, Macklaim JM, Bisanz JE, et al. Vaginal microbiome and epithelial gene array in post-menopausal women with moderate to severe dryness. *PLoS One*. 2011;6(11):e26602.
95. Aagaard K, Riehle K, Ma J, et al. A metagenomic approach to characterization of the vaginal microbiome signature in pregnancy. *PLoS One*. 2012;7(6):e36466.
96. De Seta F, Parazzini F, De Leo R, et al. Lactobacillus plantarum P17630 for preventing Candida vaginitis recurrence: a retrospective comparative study. *Eur J Obstet Gynecol Reprod Biol*. 2014;182:136-139.
97. Mailander-Sanchez D, Wagener J, Schaller M. Potential role of probiotic bacteria in the treatment and prevention of localised candidosis. *Mycoses*. 2012;55(1):17-26.
98. Martinez RC, Seney SL, Summers KL, Nomizo A, De Martinis EC, Reid G. Effect of Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 on the ability of Candida albicans to infect cells and induce inflammation. *Microbiol Immunol*. 2009;53(9):487-495.
99. Pendharkar S, Brandsborg E, Hammarstrom L, Marcotte H, Larsson PG. Vaginal colonisation by probiotic lactobacilli and clinical outcome in women conventionally treated for bacterial vaginosis and yeast infection. *BMC Infect Dis*. 2015;15:255.
100. Davidson F, Oates JK. The pill does not cause 'thrush'. *Br J Obstet Gynaecol*. 1985;92(12):1265-1266.
101. Ismail AM, Abbas AM, Shams AH, Kamel MA, Makarem MH. The effect of use of vaginal LActobacillus rhamnosus for prevention of recurrence of vulvovaginal candidiasis: a randomized controlled trial. *Thai J Obstet Gynaecol*. 2017;25:62-68.
102. Cruickshank JG, Gelfand M. Superadded bacterial infection in acute and chronic forms of urinary bilharziasis. *Central Afr J Med*. 1977;23(11 Suppl):16-18.
103. Santos CMA, Pires MCV, Leão TL, et al. Selection of Lactobacillus strains as potential probiotics for vaginitis treatment. *Microbiology*. 2016;162(7):1195-1207.
104. Fischer G, Bradford J. Vulvovaginal candidiasis in postmenopausal women: the role of hormone replacement therapy. *J Low Genit Tract Dis*. 2011;15(4):263-267.
105. Kalo-Klein A, Witkin SS. Candida albicans: cellular immune system interactions during different stages of the menstrual cycle. *Am J Obstet Gynecol*. 1989;161(5):1132-1136.
106. Gaspard U, Scheen A, Endrikat J, et al. A randomized study over 13 cycles to assess the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on carbohydrate metabolism. *Contraception*. 2003;67(6):423-429.
107. Foxman B. The epidemiology of vulvovaginal candidiasis: risk factors. *Am J Public Health*. 1990;80(3):329-331.
108. van de Wijgert JH, Verwijs MC, Turner AN, Morrison CS. Hormonal contraception decreases bacterial vaginosis but oral contraception may increase candidiasis: implications for HIV transmission. *AIDS (London, England)*. 2013;27(13):2141-2153.
109. Spacek J, Kestranek J, Jilek P, Lesko D, Plucnarova S, Buchta V. Comparison of two long-term gestagen regimens in the management of recurrent vulvovaginal candidiasis: A pilot study. *Mycoses*. 2017;60(4):260-265.
110. Babula O, Lazdane G, Kroica J, Linhares IM, Ledger WJ, Witkin SS. Frequency of interleukin-4 (IL-4) -589 gene polymorphism and vaginal concentrations of IL-4, nitric oxide, and mannose-binding lectin in women with recurrent vulvovaginal candidiasis. *Clin Infect Dis*. 2005;40(9):1258-1262.

111. Donders GG, Babula O, Bellen G, Linhares IM, Witkin SS. Mannose-binding lectin gene polymorphism and resistance to therapy in women with recurrent vulvovaginal candidiasis. *BJOG*. 2008;115(10):1225-1231.
112. Chaim W, Foxman B, Sobel JD. Association of recurrent vaginal candidiasis and secretory ABO and Lewis phenotype. *J Infect Dis*. 1997;176(3):828-830.
113. Ferwerda B, Ferwerda G, Plantinga TS, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. *N Engl J Med*. 2009;361(18):1760-1767.
114. Cassone A, Casadevall A. Recent progress in vaccines against fungal diseases. *Curr Opin Microbiol*. 2012;15(4):427-433.
115. de Jong MA, Vriend LE, Theelen B, et al. C-type lectin Langerin is a beta-glucan receptor on human Langerhans cells that recognizes opportunistic and pathogenic fungi. *Mol Immunol*. 2010;47(6):1216-1225.
116. Holland SM, Vinh DC. Yeast infections–human genetics on the rise. *N Engl J Med*. 2009;361(18):1798-1801.
117. Romani L. Immunity to fungal infections. *Nat Rev Immunol*. 2004;4(1):1-23.
118. Vecchiarelli A, Pericolini E, Gabrielli E, Pietrella D. New approaches in the development of a vaccine for mucosal candidiasis: progress and challenges. *Front Microbiol*. 2012;3:294.
119. Neves NA, Carvalho LP, De Oliveira MAM, et al. Association between atopy and recurrent vaginal candidiasis. *Clin Exp Immunol*. 2005;142(1):167-171.
120. Witkin S, Giraldo P. Linhares I. New insights into the immune pathogenesis of recurrent vulvovaginal candidiasis. *Italian J Gynaecol Obstet*. 2000;12:114-118.
121. Raska M, Belakova J, Horynova M, et al. Systemic and mucosal immunization with Candida albicans hsp90 elicits hsp90-specific humoral response in vaginal mucosa which is further enhanced during experimental vaginal candidiasis. *Med Mycol*. 2008;46(5):411-420.
122. Giraldo P, Neuer A, Korneeva IL, Ribeiro-Filho A, Simoes JA, Witkin SS. Vaginal heat shock protein expression in symptom-free women with a history of recurrent vulvovaginitis. *Am J Obstet Gynecol*. 1999;180(3 Pt 1):524-529.
123. Rylander E, Berglund AL, Krassny C, Petrini B. Vulvovaginal candida in a young sexually active population: prevalence and association with oro-genital sex and frequent pain at intercourse. *Sex Transm Infect*. 2004;80(1):54-57.
124. Reed BD, Zazove P, Pierson CL, Gorenflo DW, Horrocks J. Candida transmission and sexual behaviors as risks for a repeat episode of Candida vulvovaginitis. *J Womens Health (Larchmt)*. 2003;12(10):979-989.
125. Ehrstrom SM, Kornfeld D, Thuresson J, Rylander E. Signs of chronic stress in women with recurrent candida vulvovaginitis. *Am J Obstet Gynecol*. 2005;193(4):1376-1381.
126. Meyer H, Goettlicher S, Mendling W. Stress as a cause of chronic recurrent vulvovaginal candidosis and the effectiveness of the conventional antimycotic therapy. *Mycoses*. 2006;49:202-209.
127. Cruickshank R. Acquired immunity: bacterial infections. *Mod Trends Immunol*. 1963;1:107-129.
128. Anderson MR. Evaluation of vaginal complaints. *JAMA*. 2004;291.
129. Mendling W, Niemann D, Tintelnot K. Vaginal colonisation with Candida species with special focus on *Candida dubliniensis*. A prospective study. *Geburtshilfe Frauenheilkd*. 2007;67(10):1132-1137.
130. Spacek J. Jilek P, Buchta V. The serum levels of calcium, magnesium, iron and zinc in patients with recurrent vulvovaginal candidosis during attack, remission and in healthy controls.*Mycoses*. 2005;48:391-395.
131. Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. *JAMA*. 2004;291(11):1368-1379.
132. Beghini J, Linhares IM, Giraldo PC, Ledger WJ, Witkin SS. Differential expression of lactic acid isomers, extracellular matrix metalloproteinase inducer, and matrix metalloproteinase-8 in vaginal fluid from women with vaginal disorders. *BJOG*. 2015;122(12):1580-1585.
133. Falsetta ML, Foster DC, Woeller CF, et al. Identification of novel mechanisms involved in generating localized vulvodynia pain. *Am J Obstet Gynecol*. 2015;213(1):38.e1-38.e12.
134. Fidel PL Jr, Vazquez JA, Sobel JD *Candida glabrata*: review of epidemiology, pathogenesis, and clinical disease with comparison to *C albicans*. *Clin Microbiol Rev*. 1999;12(1):80-96.
135. Mendling W. Torulopsis in gynecology. *Geburtshilfe Frauenheilkd*. 1984;44(9):583-586.
136. Sobel JD. Vulvovaginitis due to Candida glabrata. *An emerging problem Mycoses*. 1998;41:18-22.
137. Spinillo A, Capuzzo E, Egbe TO, Baltaro F, Nicola S, Piazzi G. Torulopsis glabrata vaginitis. *Obstet Gynecol*. 1995;85(6):993-998.
138. Singh S, Sobel JD, Bhargava P, Boikov D, Vazquez JA. Vaginitis due to candida krusei: epidemiology. Clinical apsects, and therapy. *Clin Infect Dis*. 2002;35(9):1066-1070.
139. Pea N. Vaginal Candida parapsilsosis - pathogen or bystander? *Infect Dis Obstet Gynecol*. 2005;13:37-41.
140. Savini V, Catavitello C, Manna A, et al. Two cases of vaginitis caused by itraconazole-resistant Saccharomyces cerevisiae and a review of recently published studies. *Mycopathologia*. 2008;166(1):47-50.
141. Farmer MA, Taylor AM, Bailey AL, et al. Repeated vulvovaginal fungal infections cause persistent pain in a mouse model of vulvodynia. *Sci Transl Med*. 2011;3(101):101ra91.
142. Aballéa S, Guelfucci F, Wagner J, et al. Subjective health status and health-related quality of life among women with Recurrent Vulvovaginal Candidosis (RVVC) in Europe and the USA. *Health Qual Life Outcomes*. 2013;11:169.
143. Lowe NK, Neal JL, Ryan-Wenger NA. Accuracy of the clinical diagnosis of vaginitis compared with a DNA probe laboratory standard. *Obstet Gynecol*. 2009;113(1):89-95.
144. Müller J, Nold B, Kubitza D, Baumert JJGT. *Monographie*. Amsterdam, Oxford, Princeton: Excerpta Medica. Quantitative Untersuchungen über die Döderlein-Flora gesunder sowie mykosekranker Probandinnen unter lokaler Isoconazol-Nitrat-Therapie. 1981:81–93.
145. Mylonas I, Bergauer F. Diagnosis of vaginal discharge by wet mount microscopy: a simple and underrated method. *Obstet Gynecol Surv*. 2011;66(6):359-368.
146. Nyirjesy P, Seeney SM, Grody MH, Jordan CA, Buckley HR. Chronic fungal vaginitis: the value of cultures. *Am J Obstet Gynecol*. 1995;173(3 Pt 1):820-823.
147. Hoffstetter SE, Barr S, LeFevre C, Leong FC, Leet T. Self-reported yeast symptoms compared with clinical wet mount analysis and vaginal yeast culture in a specialty clinic setting. *J Reprod Med*. 2008;53(6):402-406.
148. Mulhem E, Boyanton BL Jr, Robinson-Dunn B, Ebert C, Dzebo R. Performance of the Affirm VP-III using residual vaginal discharge collected from the speculum to characterize vaginitis in symptomatic women. *J Low Genit Tract Dis*. 2014;18(4):344-346.
149. Bradford LL, Chibucos MC, Ma B, Bruno V, Ravel J. Vaginal Candida spp. genomes from women with vulvovaginal candidiasis. *Pathog Dis*. 2017;75(6).
150. Wilson C. Recurrent vulvovaginitis candidiasis; an overview of traditional and alternative therapies. *Adv Nurse Pract*. 2005;13(5):24-29; quiz 30.
151. Plempel M. Pharmacokinetics of imidazole-antimycotics (author's transl). *Mykosen*. 1980;23(1):16-27.
152. Scheklakow ND, Delektorski WW, Golodova OA. Ultrastructural changes in *Candida albicans* caused by polyene antibiotics (author's transl). *Mykosen*. 1981;24(3):140-152.
153. Niewerth M, Kunze D, Seibold M, Schaller M, Korting HC, Hube B. Ciclopirox olamine treatment affects the expression pattern of Candida albicans genes encoding virulence factors, iron

metabolism proteins, and drug resistance factors. *Antimicrob Agents Chemother*. 2003;47(6):1805-1817.
154. W. M. Azoles in the therapy of vaginal candidosis. 1988:480–506.
155. Workowski KA, Bolan GA. Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep*. 2015;64(RR-03):1-137.
156. Fan S, Liu X, Liang Y. Miconazole nitrate vaginal suppository 1,200 mg versus oral fluconazole 150 mg in treating severe vulvovaginal candidiasis. *Gynecol Obstet Invest*. 2015;80(2):113-118.
157. Wajnberg M, Wajnberg A. A comparative double blind trial with vaginal creams of cyclopyroxolamine and miconazole in vulvovaginal candidosis (author's transl). *Mykosen*. 1981;24(12):721-730.
158. Zhou X, Li T, Fan S, et al. The efficacy and safety of clotrimazole vaginal tablet vs. oral fluconazole in treating severe vulvovaginal candidiasis. *Mycoses*. 2016;59(7):419-428.
159. Nurbhai M, Grimshaw J, Watson M, Bond C, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database Syst Rev*. 2007;4:CD002845.
160. Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. *N Engl J Med*. 2004;35:875-883.
161. Cohen L. Is more than one application of an antifungal necessary in the treatment of acute vaginal candidiasis? *Am J Obstet Gynecol*. 1985;152(7 Pt 2):961-964.
162. Quereux C, Gelas B, Chevallier T, Petit F, Micheletti MC. Evaluation of the efficacity and speed of action of sertaconazole nitrate suppository and cream combined treatment for vulvovaginal candidiasis. *Gynecologie, obstetrique & fertilite*. 2000;28(3):238-244.
163. Mendling W, Schlegelmilch R. Three-day combination treatment for vulvovaginal candidosis with 200 mg clotrimazol vaginal suppositories and clotrimazol cream for the vulva is significantly better than treatment with vaginal suppositories alone – an earlier, multi-centre, placebo-controlled double blind study. *Geburtshilfe Frauenheilkd*. 2014;74(4):355-360.
164. Donders GG, Sobel JD. Candida vulvovaginitis: a store with a buttery and a show window. *Mycoses*. 2017;60(2):70-72.
165. Mendling W, Weissenbacher ER, Gerber S, Prasauskas V, Grob P. Use of locally delivered dequalinium chloride in the treatment of vaginal infections: a review. *Arch Gynecol Obstet*. 2016;293(3):469-484.
166. Della Casa V, Noll H, Gonser S, Grob P, Graf F, Pohlig G. Antimicrobial activity of dequalinium chloride against leading germs of vaginal infections. *Arzneimittelforschung*. 2002;52(9):699-705.
167. Friese K, Neumann G, Siebert J. Topical antiseptics as an alternative in the treatment of acute vulvovaginal candidosis. *Arch Gynecol Obstet*. 2003;268(3):194-197.
168. Frey TB. Antimicrobial topical agents used in the vagina. *Curr Probl Dermatol*. 2011;40:36-47.
169. Buch A, Skytte CE. Treatment of vaginal candidosis with natamycin and effect of treating the partner at the same time. *Acta Obstet Gynecol Scand*. 1982;61(5):393-396.
170. Bisschop MP, Merkus JM, Scheygrond H, van Cutsem J. Co-treatment of the male partner in vaginal candidosis: a double-blind randomized control study. *Br J Obstet Gynaecol*. 1986;93(1):79-81.
171. Thoden J, Potthoff A, Bogner JR, et al. Therapy and prophylaxis of opportunistic infections in HIV-infected patients: a guideline by the German and Austrian AIDS societies (DAIG/OAG) (AWMF 055/066). *Infection*. 2013;41(Suppl 2):S91-115.
172. Alczuk Sde S, Bonfim-Mendonca Pde S, Rocha-Brischiliari SC, et al. Effect of highly active antiretroviral therapy on vaginal *Candida* spp. isolation in HIV-infected compared to HIV-uninfected women. *Rev Inst Med Trop Sao Paulo*. 2015;57(2):169-174.
173. das Neves J, Pinto E, Teixeira B, et al. Local treatment of vulvovaginal candidosis : general and practical considerations. *Drugs*. 2008;68(13):1787-1802.
174. Richter SS, Galask RP, Messer SA, Hollis RJ, Diekema DJ, Pfaller MA. Antifungal susceptibilities of *Candida* species causing vulvovaginitis and epidemiology of recurrent cases. *J Clin Microbiol*. 2005;43(5):2155-2162.
175. Mathema B, Cross E, Dun E. Prevalence of vaginal colonization by drug-resistant candida species in college-age women with previous exposure to over the counter azole antifungals. *CID*. 2001;33:e23-e27.
176. Sobel JD, Zervos M, Reed BD, et al. Fluconazole susceptibility of vaginal isolates obtained from women with complicated Candida vaginitis: clinical implications. *Antimicrob Agents Chemother*. 2003;47(1):34-38.
177. Phillips AJ. Treatment of non-albicans *Candida vaginitis* with amphotericin B vaginal suppositories. *Am J Obstet Gynecol*. 2005;192(6):2009-2012.discussion 2012–2003.
178. Healey KR, Katiyar SK, Castanheira M, Pfaller MA, Edlind TD. Candida glabrata mutants demonstrating paradoxical reduced caspofungin susceptibility but increased micafungin susceptibility. *Antimicrob Agents Chemother*. 2011;55(8):3947-3949.
179. Gilfillan GD, Sullivan DJ, Haynes K, Parkinson T, Coleman DC, Gow NA. *Candida dubliniensis*: phylogeny and putative virulence factors. *Microbiology (Reading)*. 1998;144(Pt 4):829-838.
180. Moran GP, Sanglard D, Donnelly SM, Shanley DB, Sullivan DJ, Coleman DC. Identification and expression of multidrug transporters responsible for fluconazole resistance in *Candida dubliniensis*. *Antimicrob Agents Chemother*. 1998;42(7):1819-1830.
181. Sobel JD. Management of recurrent vulvovaginal candidiasis with intermittent ketoconazole prophylaxis. *Obstet Gynecol*. 1985;65(3):435-440.
182. Davidson F, Mould RF. Recurrent genital candidosis in women and the effect of intermittent prophylactic treatment. *Br J Vener Dis*. 1978;54(3):176-183.
183. Roth AC, Milsom I, Forssman L, Wahlen P. Intermittent prophylactic treatment of recurrent vaginal candidiasis by postmenstrual application of a 500 mg clotrimazole vaginal tablet. *Genitourin Med*. 1990;66(5):357-360.
184. Sobel JD. Recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol*. 2016;214(1):15-21.
185. Donders GG, Bellen G, Mendling W. Management of recurrent vulvo-vaginal candidosis as a chronic illness. *Gynecol Obstet Invest*. 2010;70(4):306-321.
186. Donders G, Bellen G, Byttebier G, et al. Individualized decreasing-dose maintenance fluconazole regimen for recurrent vulvovaginal candidiasis (ReCiDiF trial). *Am J Obstet Gynecol*. 2008;199(6):e611-e619.
187. Donders GGG, Grinceviciene S, Bellen G, Jaeger M, Ten Oever J, Netea MG. Is non-response to fluconazole maintenance therapy for recurrent *Candida vaginitis* related to sensitization to atopic reactions? *Am J Reprod Immunol*. 2018;79(4):e12811.
188. Grinceviciene S, Ruban K, Bellen G, Donders GGG. Sexual behaviour and extra-genital colonisation in women treated for recurrent Candida vulvo-vaginitis. *Mycoses*. 2018;61(11):857-860.
189. Cakiroglu Y, Caliskan S, Doger E, Ozcan S, Caliskan E. Does removal of CU-IUD in patients with biofilm forming candida really maintain regression of clinical symptoms? *J Obstet Gynaecol*. 2015;35(6):600-603.
190. Hay P, Czeizel AE. Asymptomatic trichomonas and candida colonization and pregnancy outcome. *Best Pract Res Clin Obstet Gynaecol*. 2007;21(3):403-409.
191. Brand SR, Degenhardt TP, Person K, et al. A phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of orally administered VT-1161 in

the treatment of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol*. 2018;218(6):624 e621-624 e629.
192. Czeizel AE, Toth M, Rockenbauer M. No teratogenic effect after clotrimazole therapy during pregnancy. *Epidemiology*. 1999;10(4):437-440.
193. Czeizel AE, Fladung B, Vargha P. Preterm birth reduction after clotrimazole treatment during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2004;116(2):157-163.
194. Czeizel AE, Puho EH, Kazy Z. The use of data set of the Hungarian case-control surveillance of congenital abnormalities for evaluation of birth outcomes beyond birth defects. *Cent Eur J Public Health*. 2007;15(4):147-153.
195. Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. *BMJ*. 2004;329(7462):371.
196. Roberts CL, Rickard K, Kotsiou G, Morris JM. Treatment of asymptomatic vaginal candidiasis in pregnancy to prevent preterm birth: an open-label pilot randomized controlled trial. *BMC Pregnancy Childbirth*. 2011;11:18.
197. Farr A, Kiss H, Holzer I, Husslein P, Hagmann M, Petricevic L. Effect of asymptomatic vaginal colonization with Candida albicans on pregnancy outcome. *Acta Obstet Gynecol Scand*. 2015;94(9):989-996.
198. Holzer I, Farr A, Kiss H, Hagmann M, Petricevic L. The colonization with *Candida* species is more harmful in the second trimester of pregnancy. *Arch Gynecol Obstet*. 2017;295(4):891-895.
199. Blaschke-Hellmessen R. Epidemiological studies of the occurrence of yeasts in children and their mothers. *Mykosen*. 1968;11(9):611-616.
200. Blaschke-Hellmessen R. Subpartale Übertragung von Candida und ihre Konsequenzen.*Mycoses*. 1998;41:31-36.
201. Schnell JD. Epidemiology and the prevention of peripartal mycoses. *Chemotherapy*. 1982;28(Suppl 1):66-72.
202. Mendling W, Spitzbart H. Antimykotische Therapie der vaginalen Hefepilz-Kolonisation von Schwangeren zur Verhütung von Kandidamykosen beim Neugeborenen. *AMWF*, *Guideline*, 2008;15(042):S1.
203. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. 1996;175(6):1645-1650.
204. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. 2013;369(9):830-839.
205. Molgaard-Nielsen D, Svanstrom H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA*. 2016;315(1):58-67.
206. Howley MM, Carter TC, Browne ML, et al. Fluconazole use and birth defects in the National Birth Defects Prevention Study. *Am J Obstet Gynecol*. 2016;657.e1-657.e9.
207. Walker PPRM, Ashbee HR. Vaginal yeasts in the era of "over the counter" antifungals. *Sex Transm Infect*. 2000;76:437-438.
208. Ferris DG, Nyirjesy P, Sobel JD, Soper D, Pavletic A, Litaker MS. Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis. *Obstet Gynecol*. 2002;99(3):419-425.
209. Mardh PA, Novikova N, Stukalova E. Colonisation of extragenital sites by Candida in women with recurrent vulvovaginal candidosis. *BJOG*. 2003;110(10):934-937.
210. Russo R, Superti F, Karadja E, De Seta F. Randomised clinical trial in women with Recurrent Vulvovaginal Candidiasis: efficacy of probiotics and lactoferrin as maintenance treatment. *Mycoses*. 2019;62(4):328-335.
211. Hilton E, Isenberg HD, Alperstein P, France K, Borenstein MT. Ingestion of yogurt containing *Lactobacillus acidophilus* as prophylaxis for candidal vaginitis. *Ann Intern Med*. 1992;116(5):353-357.
212. Jeavons HS. Prevention and treatment of vulvovaginal candidiasis using exogenous Lactobacillus. *J Obstet Gynecol Neonatal Nurs*. 2003;32(3):287-296.
213. Falagas ME, Betsi GI, Athanasiou S. Probiotics for prevention of recurrent vulvovaginal candidiasis: a review. *J Antimicrob Chemother*. 2006;58(2):266-272.
214. Pirotta M, Gunn J, Chondros P, et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. *BMJ*. 2004;329(7465):548.
215. Witt A, Kaufmann U, Bitschnau M, et al. Monthly itraconazole versus classic homeopathy for the treatment of recurrent vulvovaginal candidiasis: a randomised trial. *BJOG*. 2009;116(11):1499-1505.
216. Crompton R, Williams H, Ansell D, et al. Oestrogen promotes healing in a bacterial LPS model of delayed cutaneous wound repair. *Lab Invest*. 2016;96(4):439-449.
217. Chew SY, Cheah YK, Seow HF, Sandai D, Than LT. Probiotic *Lactobacillus rhamnosus* GR-1 and Lactobacillus reuteri RC-14 exhibit strong antifungal effects against vulvovaginal candidiasis-causing *Candida glabrata* isolates. *J Appl Microbiol*. 2015;118(5):1180-1190.
218. Kosgey JC, Jia L, Fang Y, et al. Probiotics as antifungal agents: experimental confirmation and future prospects. *J Microbiol Methods*. 2019;162:28-37.
219. Sobel JD, Chaim W, Nagappan V, Leaman D. Treatment of vaginitis caused by *Candida glabrata*: use of topical boric acid and flucytosine. *Am J Obstet Gynecol*. 2003;189(5):1297-1300.
220. Sobel JD, Chaim W. Treatment of *Torulopsis glabrata* vaginitis: retrospective review of boric acid therapy. *Clin Infect Dis*. 1997;24(4):649-652.
221. Capoci IR, Bonfim-Mendonca Pde S, Arita GS, et al. Propolis is an efficient fungicide and inhibitor of biofilm production by vaginal *Candida albicans*. *Evid Based Complement Alternat Med*. 2015;2015:287693.
222. Ahangari F, Farshbaf-Khalili A, Javadzadeh Y, Adibpour M, Sadeghzadeh OB. Comparing the effectiveness of *Salvia officinalis*, clotrimazole and their combination on vulvovaginal candidiasis: a randomized, controlled clinical trial. *J Obstet Gynaecol Res*. 2019;45(4):897-907.
223. Huang Y, Merkatz RB, Hillier SL, et al. Effects of a one year reusable contraceptive vaginal ring on vaginal microflora and the risk of vaginal infection: an open-label prospective evaluation. *PLoS ONE*. 2015;10(8):e0134460.
224. Rosedale N, Browne K. Hyposensitisation in the management of recurring vaginal candidiasis. *Ann Allergy*. 1979;43(4):250-253.
225. Mendling WKU. Investigations by cell-mediated immunologi Tests therapeutic trials with thymopentin. *Infect Dis Obstet Gynecol*. 1996.
226. Koldowsky H, Kariger U, Mendling W. Herstellung eines autologen membrangebundenen Candida-Antigens und in-vitro-Untersuchungen zu seinen immunologischen Reaktionen. *Candida-Infektionen des weiblichen Genitaltraktes*. 1999;25-32.
227. Morschhauser J, Ruhnke M, Michel S, Hacker J. Identification of CARE-2-negative Candida albicans isolates as Candida dubliniensis. *Mycoses*. 1999;42(1–2):29-32.
228. Conti PC, Pinto-Fiamengui LM, Cunha CO, Conti AC. Orofacial pain and temporomandibular disorders: the impact on oral health and quality of life. *Braz Oral Res*. 2012;26(Suppl 1):120-123.
229. Rigg D, Miller MM, Metzger WJ. Recurrent allergic vulvovaginitis: treatment with Candida albicans allergen immunotherapy. *Am J Obstet Gynecol*. 1990;162(2):332-336.
230. Moraes PS, de Lima GS, Taketomi EA. *Candida albicans* allergen immunotherapy in recurrent vaginal candidiasis. *J Investig Allergol Clin Immunol*. 2000;10(5):305-309.
231. Rusch K, Schwiertz A. Candida autovaccination in the treatment of vulvovaginal Candida infections. *Int J Gynaecol Obstet*. 2007;96(2):130.

232. Babula O, Lazdāne G, Kroica J, et al. Frequency of interleukin-4 (IL-4) - 589 gene polymorphism and vaginal concentrations of IL-4, nitric oxide and mannose-binding lectin in women with recurrent vulvovaginal candidiasis. *CID*. 2005;40(9):1258-1262.
233. Ip WK, Lau YL. Role of mannose-binding lectin in the innate defense against candida albicans: enhancement of complement activation but lack of opsonic function, in phagocytosis by human dendritic cells. *JID*. 2004;190(3):632-640.
234. Mendling W, Koldovsky U. Investigations by cell-mediated immunologic tests and therapeutic trials with thymopentin in vaginal mycoses. *Infect Dis Obstet Gynecol*. 1996;4:225-231.
235. Weissenbacher TM, Witkin SS, Gingelmaier A, Scholz C, Friese K, Mylonas I. Relationship between recurrent vulvovaginal candidosis and immune mediators in vaginal fluid. *Eur J Obstet Gynecol Reprod Biol*. 2009;144(1):59-63.
236. Wozniak KL, Palmer G, Kutner R, Fidel PL Jr. Immunotherapeutic approaches to enhance protective immunity against Candida vaginitis. *Med Mycol*. 2005;43(7):589-601.
237. Cassone A, De Bernardis F, Torososantucci A. An outline of the role of anti-Candida antibodies within the context of passive immunization and protection from candidiasis. *Curr Mol Med*. 2005;5(4):377-382.
238. Schmidt CS, White CJ, Ibrahim AS, et al. NDV-3, a recombinant alum-adjuvanted vaccine for Candida and *Staphylococcus aureus*, is safe and immunogenic in healthy adults. *Vaccine*. 2012;30(52):7594-7600.
239. Edwards JE Jr, Schwartz MM, Schmidt CS, et al. A fungal immunotherapeutic vaccine (NDV-3A) for treatment of recurrent vulvovaginal candidiasis-a phase 2 randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2018;66(12):1928-1936.
240. Wilson D. A tale of two yeasts: *Saccharomyces cerevisiae* as a therapeutic against candidiasis. *Virulence*. 2017;8(1):15-17.
241. Cruickshank J. An Address on the bacterial flora of the intestine in health and in chronic disease. *Br Med J*. 1928;2(3534):555-558.
242. Dolphin A, Cruickshank R. Penicillin therapy in acute acterial endocarditis. *Br Med J*. 1945;1(4408):897-901.
243. Franz R, Ruhnke M, Morschhauser J. Molecular aspects of fluconazole resistance development in *Candida albicans*. *Mycoses*. 1999;42(7–8):453-458.

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