mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Guideline

Guideline: Vulvovaginal Candidosis (AWMF 015/072), S2k (excluding chronic mucocutaneous candidosis)*

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Summary

The oestrogenised vagina is colonised by *Candida* species in at least 20% of women; in late pregnancy and in immunosuppressed patients, this increases to at least 30%. In most cases, *Candida albicans* is involved.

Host factors, particularly local defence mechanisms, gene polymorphisms, allergies, serum glucose levels, antibiotics, psycho-social stress and oestrogens influence the risk of candidal vulvovaginitis. Non-*albicans* species, particularly *Candida glabrata*, and in rare cases also *Saccharomyces cerevisiae*, cause less than 10% of all cases of vulvovaginitis with some regional variation; these are generally associated with milder signs and symptoms than normally seen with a *C. albicans*-associated vaginitis.

Typical symptoms include premenstrual itching, burning, redness and odourless discharge. Although itching and redness of the introitus and vagina are typical symptoms, only 35–40% of women reporting genital itching in fact suffer from vulvovaginal candidosis.

Medical history, clinical examination and microscopic examination of vaginal content using 400× optical magnification, or preferably phase contrast microscopy, are essential for diagnosis. In clinically and microscopically unclear cases and in chronically recurring cases, a fungal culture for pathogen determination should be performed. In the event of non-*C. albicans* species, the minimum inhibitory concentration (MIC) should also be determined.

Chronic mucocutaneous candidosis, a rarer disorder which can occur in both sexes, has other causes and requires different diagnostic and treatment measures.

Treatment with all antimycotic agents on the market (polyenes such as nystatin; imidazoles such as clotrimazole; and many others including ciclopirox olamine) is easy to administer in acute cases and is successful in more than 80% of cases. All vaginal preparations of polyenes, imidazoles and ciclopirox olamine and oral triazoles (fluconazole, itraconazole) are equally effective (Table 4); however, oral triazoles should not be administered during pregnancy according to the manufacturers. *C. glabrata* is not sufficiently sensitive to the usual dosages of antimycotic agents approved for gynaecological use. In other countries, vaginal suppositories of boric acid (600 mg, 1–2 times daily for 14 days) or flucytosine are recommended. Boric acid treatment is not allowed in Germany and flucytosine is not available. Eight hundred-milligram oral fluconazole per day for 2–3 weeks is therefore recommended in Germany. Due to the clinical persistence of *C. glabrata* despite treatment with high-dose fluconazole, oral posaconazole and, more recently, echinocandins such as micafungin are under discussion; echinocandins are very expensive, are not approved for this indication and are not supported by clinical evidence of their efficacy. In cases of vulvovaginal candidosis, resistance to *C. albicans* does not play a significant role in the use of polyenes or azoles.

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Candida krusei is resistant to the triazoles, fluconazole and itraconazole. For this reason, local imidazole, ciclopirox olamine or nystatin should be used. There are no studies to support this recommendation, however. Side effects, toxicity, embryotoxicity and allergies are not clinically significant. Vaginal treatment with clotrimazole in the first trimester of a pregnancy reduces the rate of premature births.
Although it is not necessary to treat a vaginal colonisation of *Candida* in healthy women, vaginal administration of antimycotics is often recommended in the third trimester of pregnancy in Germany to reduce the rate of oral thrush and napkin dermatitis in healthy full-term newborns.
Chronic recurrent vulvovaginal candidosis continues to be treated in intervals using suppressive therapy as long as immunological treatments are not available. The relapse rate associated with weekly or monthly oral fluconazole treatment over 6 months is approximately 50% after the conclusion of suppressive therapy according to current studies. Good results have been achieved with a fluconazole regimen using an initial 200 mg fluconazole per day on 3 days in the first week and a dosage-reduced maintenance therapy with 200 mg once a month for 1 year when the patient is free of symptoms and fungal infection (Table 5). Future studies should include *Candida* autovaccination, antibodies to *Candida* virulence factors and other immunological experiments. Probiotics with appropriate lactobacillus strains should also be examined in future studies on the basis of encouraging initial results. Because of the high rate of false indications, OTC treatment (self-treatment by the patient) should be discouraged.

1. Methods

1.1. Literature review

A Medline/PubMed search was conducted using the keyword 'vulvovaginal candidosis' (as of 2/2010) which produced 2886 articles; a search using the keywords 'vulvovaginal candidosis therapy studies' produced 237 reviews. All were browsed according to title and abstract; however, a few randomised and prospective controlled studies were left over.[30,31,43,70,87,108,134,145] There were only three meta-analyses or Cochrane analyses[105,150,160] and two guidelines.[13,82] For this revision, another search was conducted using the same methods to identify articles from the last 5 years (as of 10.11.2013); this revealed 357 hits, with 44 review articles and 32 clinical studies. Systematic evaluation of the literature and extraction into evidence tables were not performed due to this guideline's classification as consensus based. The literature was nonetheless critically evaluated by the participating experts.

Regarding consensus, patient participation, assessment and management of potential conflicts of interest, participation of professional societies and validity, see the Guideline Report in the annex.

2. Introduction

Vulvovaginal candidosis is an infection of the oestrogenised vagina and vestibulum which can also extend to the outer sides of the labia minora, the labia majora, the intercrural region and the perineal region. Candidosis of the cervix or endometrium remains unknown. Connatal fetal candidosis and candidal amnionitis are rare.

The terms 'vulvovaginal candidosis' and '*Candida albicans* vulvovaginitis' are preferred.[99] The suffix '-iasis' should be reserved for parasitic infections such as trichomoniasis,[69] but is unfortunately widely used in the Anglo-American literature.

3. Summary of recommendations

3.1. The diagnosis of vulvovaginal candidosis is always made based on the combined basis of medical history, clinical signs and symptoms, as well as evidence of yeast, which is normally found through microscopic examination of a native preparation of vaginal fluid (400× optical magnification, or preferably phase contrast microscopy). In uncertain, recurring and complex cases, a yeast culture is necessary to determine the species. Serological determination of antibody titres is not recommended.

3.2. Topical treatment of acute vulvovaginal candidosis can be performed for a period of 1 day to 1 week using polyene (nystatin), imidazoles or ciclopirox olamine using a number of different preparations such as vaginal tablets, suppositories or creams; oral triazoles (1-day treatment) and antimycotic creams for the vulva may also be used. All of the different treatment regimens produced similarly good clinical and mycological results. Data are limited regarding treatment with antiseptics (hexetidine, octenidine, dequalinium chloride), although there are indications of their efficacy. These substances also affect the physiological flora of the vagina.

It is not necessary to treat an asymptomatic colonisation, provided that immune suppression, concomitant disease or chronic recurring vulvovaginal candidosis are not present (see elsewhere for treatment of vaginal colonisation during pregnancy).

3.3. Topical treatment of chronically recurring *C. albicans* vulvovaginitis consists of suppressive antimycotic treatment with an oral triazole in intervals over a period of several months due to the lack of options for immunological treatment of causal factors. The best results have been achieved using the fluconazole treatment regimen developed by Donders *et al.* [30,31] (Table 5).

3.4. The typical oral and vaginal treatments for *C. albicans* are less, or barely, effective for *Candida glabrata* vaginitis. For this reason, vaginal suppositories of 600 mg boric acid once a day for 14 days are recommended in other countries. Several authors also recommend amphotericin B suppositories, vaginal application of 17% flucytosine or 800 mg oral fluconazole per day for 2–3 weeks (see also Non-*Candida albicans* vaginitis). In Germany, oral posaconazole is recommended in combination with local nystatin and/or ciclopirox olamine treatment, as well as micafungin.[144]

Candida krusei is practically resistant to fluconazole and itraconazole (also imidazole *in vitro*, but not *in vivo*) and should therefore be treated with local imidazoles, for example, clotrimazole or ciclopirox olamine (or boric acid in the USA).

3.5. In Germany, antimycotic treatment of asymptomatic vaginal *Candida* colonisation is recommended during the final 6 weeks of pregnancy to prevent vertical transmission to healthy, full-term newborns during vaginal birth. This can significantly reduce neonatal *Candida* infections attributable to maternal colonisation, which normally appear in the 2nd–4th weeks of life in more than 10% of healthy, full-term newborns (see also colonisation during pregnancy).

4. Microbiology

Candida albicans forms *in vitro* blastospores, germ tubes, pseudomycelia, true mycelia and also chlamydospores on special culture media. *Candida glabrata* appears almost exclusively as a blastospore. The formation of pseudohyphae (except *C. glabrata* and several other *Candida* species, which only appear as blastospores) indicates an infection.[83,98,133]

Candida species and strains differ in their pathogenicity (*in vitro*), so that the development of a candidosis depends on the *Candida* species and the relative strength or weakness of the host's defence mechanisms.[8]

Around 85–95% of the *Candida* species colonising the vagina in premenopausal and pregnant, asymptomatic, healthy women and in women with acute vaginal candidosis are *C. albicans*. Close relatives are *Candida stellatoidea*, which seems to be rare in vulvovaginal candidoses (Tables 1 and 2) and *Candida africana* (Table 3). Both were only identified by special diagnostic procedures.[117,128] Exact epidemiologic data are missing.

Non-*C. albicans* species, particularly *C. glabrata*, are more likely to be identified in postmenopausal, diabetic and immune-suppressed women[23,52,53,67,81,98,100] There are significant regional differences in the distribution of *Candida* species (Tables 1 and 2 as an example for Berlin) but no evidence for the increased occurrence of non-*C. albicans* species in vaginal colonisation. In a retrospective, 4-year, PCR-based study of 93 775 cervical-vaginal smears taken for the clarification of vulvovaginal candidosis, *C. albicans* was found in 89%, *C. glabrata* in 7.9% and other *Candida* species in less than 2% of samples[147]; similar incidences were found in German[80,81] (Table 3) and British studies.[55]

Candida krusei, Candida guilliermondii, Candida tropicalis, Candida parapsilosis and other species can cause

Table 1 *Candida* colonisation of the vagina in healthy women.[81]

Species	HIV-neg. (n = 383)	100%		HIV-pos. (n = 66)	100%
Candida positive	88	22.9	P = 0.02	24	36.4
All	88	100		24	100
C. albicans	77	87.5		14	58.3
C. glabrata	6	6.8		8	33.3
C. krusei	2	2.3		0	0
C. dubliniensis	1	1.1	P = 0.001	0	0
C. parapsilosis	1	1.1		1	4.2
C. famata	1	1.1		0	0
C. magnoliae				1	4.2

Table 2 Distribution of vaginal *Candida* species in HIV-negative colonised women.[81]

Patients	Premenopausal		Postmenopausal		Pregnant		Not pregnant	
All	n = 338		n = 45		n = 192		n = 146	
with positive culture	n = 92 (23.3%)		n = 6 (13.3%)		n = 52 (27.1%)		n = 30 (20.5%)	
	P = 0.003				P = 0.02			
	n	%	n	%	n	%	n	%
C. albicans	75	91.5	2	33.3	48	92.3	27	90.0
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	–	0	–	1	3.3

Table 3 Distribution of *Candida* species in 472 cases of acute vaginal candidosis in Poland and Germany.[80]

	n	%
Acute *Candida* vulvovaginitis	472	100
C. albicans	450	95.3
C. glabrata	10	2.1
C. krusei	4	0.9
other (*C. tropicalis, C. kefyr, C. africana, S. cerevisiae*)	11	2.3

vulvovaginitis with typical symptoms in individual cases.[81,97,129,133,138]

Saccharomyces cerevisiae very rarely causes vaginal complaints[83,131] but has been identified asymptomatically in 1–2% of vaginal cultures.[81,100]

Different genotypes of *C. albicans* strains have been identified in asymptomatic women and in those with acute *Candida vaginitis*.[68] Identical *C. albicans* strains could be identified in the oro-intestinal tract and in the vagina of the same woman, as well as the sperm of her asymptomatic partner using PCR.[79]

5. Virulence factors of *C. albicans*

The first step between colonisation and infection is the attachment of the *Candida* cell to the vaginal wall with the help of mannoproteins.[38,135,142]

The capacity to form pseudohyphae and the secretion of hydrolytic proteins such as secretory aspartate proteinases (Sap 1–10) are probably the most significant virulence factors.[7,92,120] These correlate with pathogenicity.[16,51]

Siderophores enable the use of the host's iron.[50,60] Additional host factors are a strong pH tolerance of 2–11[75] and enzymes which enable *C. albicans* to survive in macrophages.[66]

Bacteria and fungi can form biofilms in which they are highly organised in a matrix substance either alone or symbiotically, and protected. Auler *et al.* [4] and Chassot *et al.* [21] describe a biofilm phenomenon involving *C. albicans* on intrauterine pessaries. In systematic examinations of women with vulvovaginal candidosis in Berlin and China using a clear definition of biofilm, no *Candida* biofilms were found in numerous vaginal tissue samples; the well-known phenomenon that *Candida* pseudohyphae penetrate vaginal tissue 8–10 cell layers deep[126] and that numerous other bacteria in abnormal vaginal flora enable penetration was recently demonstrated in vulvovaginal candidosis using fluorescence *in situ* hybridisation.[139]

The step between colonisation and vaginitis is not yet fully understood and highlights the importance of host factors.[41] It can be said that attachment to the vaginal epithelium occurs after colonisation, and then, with the help of *Candida* virulence factors, particularly secretory aspartate proteases, invasion, infection and inflammation result.

6. Genital colonisation

On account of the oestrogenisation of the vagina[29] and the oestrogen receptors of *C. albicans*,[107,140] premenarchal girls and postmenopausal women are less frequently vaginally colonised and generally do not suffer from *C. vaginitis*. It has also been confirmed in animal tests that vaginal candidosis can only occur in sterilised animals after the administration of oestrogen. Healthy, premenopausal women who are not pregnant are vaginally colonised in approximately 20–30% of cases, at least 30% of pregnant women are colonised in the third trimester and at least 30% of immune-deficient women are found to be colonised to the extent that cultures are used for detection[81,98] (Tables 1 and 2). With PCR, the detection of a vaginal *Candida* colonisation is at least 10% higher.[152] Vaginal colonisation can vary individually from time to time.

In a longitudinal cohort study with 1248 healthy, asymptomatic young women, 70% were colonised at least once over the course of 1 year, although only 4% were colonised at all visits which took place every 3 months. Recent sexual intercourse, the injection of medroxyprogesterone acetate (an ovulation inhibitor) and simultaneous colonisation with lactobacillus and B streptococcus were identified as risk factors.[6]

The partner's sperm can be colonised with the identical *Candida* strain as in the vagina,[79] even when the partner is symptom free. *Candida* balanitis should be treated, although temporary redness of the glans after intercourse with a *Candida*-colonised woman can be also represent an allergic response to *Candida* antigens. It is not clear whether the colonisation of the partner's genital tract or the oro-intestinal tract of both partners can play a role in chronic recurring *C. vaginitis.*[133]

There is no evidence of an increase in the incidence of either acute or chronic recurring vaginal candidosis in gynaecology.

7. Predisposing host factors

Patients with diabetes mellitus suffer from vaginal candidosis more frequently and treatment is likely to fail when serum glucose levels are not normalised.[12]

Lower glucose tolerance was also found in approximately 25% more women with CRVVC than in healthy controls.[32] Obesity, in conjunction with intertrigo caused by rubbing and sweating, can contribute to candidosis in the genital area.

Although *C. glabrata* is less virulent, women with type II diabetes mellitus are more frequently colonised than healthy women.[67,109]

Vaginal *Candida* colonisation is probably not increased by modern oral contraceptives with low oestrogen levels,[28] which do not significantly influence carbohydrate metabolism.[48] This also applies to the frequency of vaginal candidosis.[44] There are some contradictory observations, however.[19,122] In a systematic review of the literature, others have observed an increase in vulvovaginal candidosis when oral contraceptives are used, although this depends on the oestrogen dosage.[153]

Women with high oestrogen levels, and particularly during pregnancy, more regularly experience vaginal *Candida* colonisation. Women who are already vaginally colonised by *Candida* species have an up to 33% higher risk of developing a vaginal candidosis after treatment with antibiotics.[34,102,104,159]

Although vaginal candidosis often occurs in women with normal lactobacillus flora, lower numbers of lactobacilli have been found in women with vaginal candidosis.[3] It is assumed meanwhile that special strains of lactobacilli (for example *Lactobacillus rhamnosus*) can play a protective role against vaginal candidosis.[71,72]

Sobel [133] emphasises the likely underestimated role of sexual activity in the recurrence of vaginal candidosis, as reinfections are frequently observed after sexual intercourse, particularly oro-genital contact.[34,111,122]

Finally, genetic factors are also responsible for recurrences; gene polymorphisms of mannose-binding lectin[5,30,31] and a non-secretor phenotype of the ABO-Lewis blood group have been identified as risk factors.[20]

Four female members of a Dutch family were affected either by recurring vulvovaginal candidosis or onychomycosis and displayed a specific mutation (loss of the last 9 amino acids in the carbohydrate recognition domain). The modified form of the lectin Dectin-1 caused by this mutation led to insufficient production of cytokines (interleukin-17, tumour necrosis factor, interleukin-6) after stimulation with beta-glucan or *C. albicans*. In contrast, phagocytosis and elimination of fungi were unaffected in these patients, which explain why a lack of Dectin-1 is not associated with fungal infections. Interestingly, symptoms appeared in the homozygotic daughters between 10 and 12 years of age, while the age of manifestation in the heterozygotic mother and father was between 40 and 55 years; this suggests both hormonal and gene-dosage effects.[40] The documented mutation is notably common in parts of Africa and Europe (3–7%).

Meanwhile deeper insights have been gained in the complex field of innate and acquired immunity. Of interest are the known factors of innate and acquired humoral immunity and the factors which should neutralise *Candida* to prevent the steps between asymptomatic colonisation, attachment and infection. Vaginal microbiota also plays a not yet sufficiently understood role. Th-1-induced dendritic T cells/Langerhans cells are supported by interleukin 12. Oral and vaginal epithelial cells are capable of differentiating the *Candida* polymorphism (colonising blastospores or infectious pseudohyphae). They then produce proinflammatory cytokines which activate neutrophils. These are not protective in the vagina, however, and cause inflammation here instead. Recently, the importance of antibodies to parts of *Candida* was (again) recognised. It was found that the antibody-producing B cells have protective effects in vaginal candidosis.[18,58,62,116,146]

Women with an atopic diathesis and type 1 allergies develop vaginal candidosis significantly more often than others.[93] The clinical symptoms of vaginal candidosis, such as redness and itching, are seen as an expression of allergic phenomena, particularly in recurring cases.[133,156]

Women with a history of recurring *C. vaginitis* express heat-shock proteins during symptom-free intervals, which can provoke similar immunological defence reactions in the same way as *Candida* cells.[49,110]

Psychosocial stress can also trigger CRVVC, likely due to immune suppression.[35,87] Vice versa, CRVVC has a considerable negative influence on the patient's professional and private life.[85]

Because infection requires both colonisation and disposition – candidosis is the infection of the infected – immune-suppressed individuals are particularly likely to develop candidosis. Seventy-five per cent of otherwise healthy women develop vulvovaginal candidosis at least once in their lives and many experience more than four episodes per year (chronic recurring vulvovaginal candidosis/CRVVC).[23,133] In an Internet questionnaire with 6000 women in five European countries and the USA, 30–50% of women in each country reported having vulvovaginal candidosis at least once, and approximately 9% suffered from CRVVC for several years.[45] Nonetheless, no correlation was found between the frequency of antibiotic prescriptions and chronic recurring vulvovaginal candidosis.

8. Clinical symptoms

Due to the influence of oestrogen, premenopausal women normally suffer primarily from vaginal candidosis, which can extend to the vulva, while postmenopausal women typically suffer from vulvar and/or intercrural candidosis. Clinical symptoms typically appear prior to menstruation: the cell proliferation induced by oestrogens and the cytolysis induced by progesterone releases glycogen, which can be metabolised by lactobacilli, increase glucose levels in the vagina.[34]

In approximately 90% of patients, itching is the most important, but not the most reliable, symptom, as only 35–40% of the women suffering from itching are found to have vaginal candidosis.[2,81,152] Discharge can range widely from fluid (often at the start of an acute vaginal candidosis) to clumpy, or in CRVVC can be entirely absent.[137] Vulvovaginal candidoses can be divided into simple and complex cases from a clinical and therapeutic standpoint.[133] The pseudohyphae used for differentiation are not always found microscopically in all cases of the so-called simple candidosis.

Most patients complain of vaginal redness, soreness, burning, dyspareunia and dysuria. These symptoms alone are not sufficient for the clinician to reliably determine the causes of an episode of vaginitis. On the other hand, itching and redness are very rarely absent in vaginal candidosis.[2] The discharge does not have an unpleasant odour in contrast to bacterial vaginosis. The inner labia can be oedematous, and burning fissures are seen particularly in CRVVC.

From a dermatological standpoint, vulvar candidosis can be divided into vesicular, eczematoid and follicular (hair follicle) forms (after Mendling and Seebacher [82]).

In severe cases, a thick layer of discharge can attach to the vaginal wall and lead to minor bleeding when removed.

Candida glabrata vaginitis is rare and generally occurs in the late prepausal and peri-pausal period.[42,55,76,132,138] *Candida krusei* vaginitis,[129] *Candida parapsilosis* vaginitis[97] and the rare *S. cerevisiae* vaginitis[83,123,131] are generally similar to *C. glabrata* vaginitis and are associated with only mild clinical symptoms.

Candida cervicitis is unknown

In comparison with the general population and using established evaluation criteria, women with CRVVC are significantly impacted in their quality of life and health status in a manner comparable to asthma or chronic obstructive bronchitis and show significantly reduced productivity in their professional and daily lives.[1]

9. Diagnosis

The diagnosis of vaginal candidosis is always made using a combination of medical history, clinical symptoms and the detection of yeast. Clinical diagnosis can be difficult, as a vulvovaginal candidosis is not necessarily present even when *Candida* has been detected and itching of the introitus occurs. In a prospective study of the accuracy of clinical diagnosis of bacterial vaginosis, trichomoniasis and vulvovaginal candidosis in 535 soldiers with vulvovaginal complaints, the sensitivity and specificity of the diagnosis using classical diagnostic methods (medical history, vaginal examination, pH-value, microscopy of native preparation) amounted to 83.8–84.8%,[70] which corresponded to the earlier results of Müller *et al.* [90], whereas

Candida could be identified in 20.9% using PCR in contrast to 14% of all women.

9.1. Necessary diagnostics

Medical history, gynaecological examination and microscopic examination of discharge using a saline solution or 10% potassium hydroxide solution under 400× optical magnification, or preferably phase contrast microscopy, are essential for diagnosis.[83,91] pH measurement can also be performed if necessary. Blastospores or (pseudo-) hyphae can be found microscopically in approximately 50–80% of vaginal candidosis cases,[90,133] although they are only microscopically visible during colonisation in approximately half of the cases. An increased number of leucocytes may be found in discharge, but this is not necessarily always the case. In the event that no blastospores or (pseudo-) hyphae can be found during microscopy or if the case is a CRVVC or is otherwise complicated, it is necessary to perform a culture to determine the species involved.[34,57,96]

Sabouraud glucose agar is the typical medium for performing diagnostic cultures. Other equally sensitive and reliable media are also available, including chrome agar for differentiation and Microstix-Candida.

It is possible that two or more different yeast species can be cultured in a case of vaginal candidosis, for example, *C. albicans* and *C. glabrata*. The patient typically suffers from a *C. albicans* vaginitis while the generally resistant *C. glabrata* remains *in situ* after treatment. It is generally only present as a colonisation and need not be treated again in the absence of symptoms.

In vitro sensitivity testing is not necessary and at most only if non-*C. albicans* species are found and the infection chronically recurs.

9.2. Unnecessary diagnostics

Serological tests are not considered useful for the diagnosis of vulvovaginal candidosis because low levels of antibodies can be found in most people's blood. Antibodies are measurable in women both with and without vaginal candidosis (e.g. due to intestinal colonisation). Superficial vaginal candidosis does not cause increased antibody levels.

10. Treatment

There are a great number of options for conventional and alternative treatments.[154] Polyenes form complexes using the ergosterol of the yeast membranes and alter their permeability.[124] Azoles hinder the conversion of lanosterol to ergosterol in the yeast cell membranes.[106] Ciclopirox olamine hinders important iron-dependent enzymes through the formation of chelate.[94]

10.1. Colonisation

Even with high bacteria counts, asymptomatic vaginal colonisation does not require treatment provided that the patient is immunocompetent and does not suffer from CRVVC.

10.2. Colonisation during pregnancy

Almost all healthy full-term newborns who are colonised with *C. albicans* during vaginal birth will develop oral thrush and/or napkin dermatitis at some point in the first year of life, peaking in the second to fourth week.[10,11]

For this reason, prophylactic treatment of asymptomatic Candida colonisation is recommended in Germany in the final weeks of pregnancy to prevent the colonisation and subsequent infection of the newborn during vaginal birth. This significantly reduces the occurrence of oral thrush and napkin dermatitis from approximately 10% to 2% in the fourth week of life.[10,84,125]

In retrospective studies,[7,24,25,26,54] and one prospective study[63] a significant reduction in premature births was found after vaginal treatment with clotrimazole in the first trimester of pregnancy. In an Australian study with a relatively small number of patients, only a non-significant reduction in premature births was observed after clotrimazole treatment in the first trimester.[115] It is under discussion whether non-*C. albicans* species, inflammatory cytokines triggered by *Candida* in the vagina, or the antibacterial components of clotrimazole play the decisive role against gram-positive coccoids. More prospective studies are therefore needed.

Since the introduction of triazoles around 1990, no neonatal deformities have been observed in the first trimester.[24,73] According to a Danish study, the administration of fluconazole in typical gynaecological dosages of 150–300 mg/day is harmless throughout pregnancy. In a cohort of 7352 pregnancies, however, seven incidences of Fallot tetralogy were found in association with the medically indicated cumulative administration of 150–6000 mg of fluconazole in the first trimester; in the control group of 968 236 pregnancies where no fluconazole was administered in the

first trimester, a significantly lower incidence was reported.[88]

10.3. Treatment of acute vulvovaginal candidosis

Acute vulvovaginal candidosis can be treated locally with polyenes (nystatin, amphotericin B), imidazoles (clotrimazole, miconazole nitrate, econazole nitrate, fenticonazole nitrate)[77,133] or ciclopirox olamine[148] (Table 4).

Vaginal suppositories and creams are available with dosages and preparations for treatment periods ranging from 1 to 3 days and 6 or 7 days and are considered harmless for patients.[114]

Oral treatment with the triazoles fluconazole and itraconazole is also possible.

The mycological and clinical success rates for the different approved treatment regimens are basically the same outside pregnancy and range from approximately 85% at 1–2 weeks and 75% at 4–6 weeks after treatment.[22,80,95,105,134]

Treatment success rates during pregnancy are significantly better with imidazoles than with polyenes.[160]

In the event that the candidosis extends to the vulvar region outside the vaginal introitus or to the inguinal region, an antimycotic skin cream, for example, clotrimazole, is recommended 2× daily for approximately 1 week. The combination of intravaginal treatment of acute vulvovaginal candidosis with additional cream for the vulva appears to produce better treatment results than intravaginal treatment alone. There are few studies available to support this, however.[86,108]

'Blind' treatment of the asymptomatic sexual partner is not beneficial for the patient.[9,14,133] No studies have been found which demonstrate a benefit for the patient from treating the asymptomatic sexual partner who is colonised on the penis or in the sperm.

Vaginal candidosis occurs much more frequently in HIV-positive women (Table 1). This problem and the multiple issues involved in treatment are examined in the HIV guidelines regarding the treatment of opportunistic infections.[141] Sexual partners of HIV-positive women should be informed of the increased risk of infection if they display a predisposition to *Candida* balanitis.

10.4. Side effects

All vaginal and local antimycotics are well tolerated. Azoles and ciclopirox olamine can cause minor local burning in 1–10% of cases.[77,80] Allergic reactions are possible but rare.

Hydrophilic fluconazole and lipophilic itraconazole rarely cause side effects in normal dosages. Itraconazole causes significantly more side effects during systemic treatment than fluconazole (e.g. anaphylactic reactions, headaches, etc.).

10.5. Resistance to *C. albicans*?

Although strains of vaginal *C. albicans* have been found with higher minimal inhibitory concentrations against fluconazole,[112] cases of azole resistance in vaginal candidosis are rare.[74,112] Clinical resistance does not correlate with minimal inhibitory concentrations and vice versa. For this reason, resistance tests are generally not recommended,[133] unless the case involves non-*C. albicans* species. Sensitivity testing should be performed in a laboratory experienced in mycology when a *C. albicans* vulvovaginitis

Table 4 Antimycotic agents against vulvovaginal candidosis.

Polyenes (since ca. 1960)
Nystatin: vaginal tablets or vaginal suppositories 100 000 IE, 200 000 IE for 6 days – treatment, nystatin cream, nystatin ointment.
Amphotericin B (no longer available in Germany for vaginal treatment)
Imidazoles (since ca. 1970)
Clotrimazole, miconazole nitrate, econazole nitrate, fenticonazole nitrate and others in the form of vaginal tablets, vaginal suppositories, vaginal creams, skin creams (for the vulva and perineal areas). For example, 500 mg clotrimazole vaginal tablets for 1-day treatment or 600 mg fenticonazole nitrate in the form of a vaginal suppository; for 3-day treatment clotrimazole 200 mg vaginal tablets or 2% vaginal cream; for 6-day treatment 100 mg clotrimazole vaginal tablets or 1% vaginal cream, etc.
Oral imidazoles (since ca. 1980)
Ketoconazole (no longer available in Germany)
Triazoles (since ca. 1990)
Fluconazole 150 mg hard capsules for 1-day treatment, fluconazole 50 mg, 100 mg, 200 mg capsules.
Itraconazole hard capsules 100 mg, 2 × 200 mg for 1-day treatment
Ciclopirox olamine (for gynaecological treatment since ca. 1995)
Vaginal cream 10 mg/g: 50 mg daily for 6 days

reappears after a longer period of chemoprophylaxis using fluconazole.[127]

10.6. Non-*C. albicans* vaginitis

Typical vaginal and oral treatments are generally unsuccessful against *C. glabrata* vaginitis. Sobel *et al.* [136] therefore recommend vaginal suppositories containing 600 mg boric acid for 14 days, while Philips [101] recommends amphotericin B. In treatment-resistant cases, vaginal treatment for 2 weeks using 17% flucytosine is successful in 90% of cases [136]. Boric acid treatment is not permitted in Germany and vaginal flucytosine preparations are not available. It was therefore recommended until recently that 800 mg fluconazole be administered orally for 2–3 weeks against *C. glabrata* vaginitis (but not colonisation!).[65,82] Even with this treatment, failures have increasingly been seen. For this reason, Tietz [143] recommended the oral administration of posaconazole together with local treatment with ciclopirox olamine and/or nystatin for 15 days on the basis of remission in 14 of 15 patients. He did begin to observe quickly emerging resistance as well as treatment failure with that regimen, however. He then described the successful treatment of 14 patients with *C. glabrata* infections of the vagina at several German universities and his own institute using micafungin, an echinocandin approved for the treatment of life-threatening mycoses, for example in haemato-oncology.[144] Such measures are only appropriate in exceptional cases involving significant illness as this is an 'off-label', non-approved use.

Candida krusei vaginitis is resistent to fluconazole and flucytosine; however, local clotrimazole, ciclopirox olamine[83,143] and (e.g. in the USA) boric acid[129] can be used. Nystatin treatment is also prone to failure. Due to the rareness of such cases, no results are available from clinical studies. There are also no studies available which compare antimycotics and antiseptics. Dequalinium chloride is effective *in vitro*,[15] while octenidine and others have at least been tested as alternatives for acute vulvovaginal candidosis.[46,47]

10.7. Chronically recurring *C. albicans* vulvovaginitis

Because infection requires colonisation and disposition and treatment of the 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.[27,119,130,134] The results are comparable regardless of whether local clotrimazole 500 mg, oral ketoconazole 100 mg or oral fluconazole 150 mg is administered. However, recurrence occurs in approximately half of all patients shortly after ending treatment.[130,134] In a placebo-controlled study with a randomised collective of 387 women who received 150 mg fluconazole weekly for 6 months, the group of illness-free women after 12 months totalled 42.9% in the fluconazole group and 21.9% in the placebo group.[134] CRVVC is therefore comparable to a chronic, incurable disease.[33]

The treatment and prophylaxis recommended by Donders *et al.* [30,31], which involves an initial dose of 3× 200 mg fluconazole in the first week, followed by a dosage-reduced maintenance regimen (Table 5), is beneficial as almost 90% of the patients were found to be illness free after 6 months and 77% of the patients remained so at 1 year. The cumulative total dose amounted to 3800 mg fluconazole in 6 months and 5000 mg in 1 year according to Donders' treatment schedule. The administration of 150 mg fluconazole per week amounts to 3600 mg after 6 months, but 7200 mg fluconazole at 1 year with the same treatment results.

Removal of intrauterine pessaries should be considered in women with recurring vulvovaginal candidosis because histology and culturing have shown that *C. albicans* is significantly more likely to attach to plastic pessaries containing levonorgestrel in women with candidosis than in women without recurrences. After removal of the IUD and treatment with fluconazole, these women did not experience recurrences for a long period of time.[161]

11. Open questions

A number of questions remain open. How and why do immunological defence mechanisms in the vagina fail in a number of women and why do they allow recurring infections and inflammation after an acute episode of vaginal candidosis?

Antimycotic agents are clearly not the answer and only improve acute symptoms in such cases.

What role does a recurring *Candida* infection of the vulva or vagina play in the development of vestibulodynia? Many women with provoked secondary vestibulodynia report vulvovaginal candidosis before the appearance of vestibular pain. In animal testing a significant correlation could be found between vulvovaginal *Candida* infections and vestibulodynia as well as incrementation of an unusual number and density of nerves in the superficial epithelial layers accompanied by significant immunohistochemical changes.[37]

Table 5 Individualised, dose-reduced maintenance treatment with fluconazole in chronically recurring vulvovaginal candidosis.[30,31]

Week 1: 200 mg fluconazole Day 1, 3 and 5	• Prerequisite for next step: Free of clinical symptoms, mycology (microscopy, culture) negative, otherwise back to first step
Weeks 2-8: 200 mg fluconazole 1x/week	• Optimal Responders: Treatment ends after 1 year without recurrence
Months 3-6: 200 mg fluconazole every 2 weeks	• Sub-optimal: Symptom-free, but recurrence or symptom-free colonization
Months 7-12: 200 mg fluconazole every 4 weeks	• Non-responders: At least two recurrences

11.1. Immunological approaches to treatment

A satisfactory immunological treatment for recurring vaginal candidosis has not yet been developed, although Rosedale and Brown [118] reported promising initial results of hyposensitisation more than 30 years ago. *In vitro* studies using autologous membrane-bound *C. albicans* antigens and T cells in a patient with chronic recurring *C. albicans* vaginitis produced better immunological responses than commercial *Candida* antigens.[64] Rigg *et al.* [113] reported a *Candida* allergen treatment, while Moraes *et al.* [89] and Rusch and Schwiertz [121] reported results from a *Candida* autovaccination, which only used allergoid components as used in hyposensitisation. There has yet to be a therapeutic breakthrough in this field, despite numerous experiments to better understand the immunopathogenicity of *C. vaginitis*.[5,7,17,41,41,59,78,93,151,155,156,158] Intramuscular injection of non-H_2O_2-forming 'aberrant' lactobacilli, which induce antibody formation and unspecific immune reactions and can be successfully used primarily against trichomoniasis and bacterial vaginosis, failed to reduce the number of recurrences of chronic recurring vulvovaginal candidosis, although it did lead to significant improvement in individual scoring with regard to physical and psychological well-being.[85]

Alongside a number of methods for inducing the production of antibodies against systemic candidosis, two vaccinations against oral and vulvovaginal candidosis have moved closer to clinical trial: one targets secretory aspartate protease 2 (Sap 2), the most important virulence factor of *C. albicans*, while the other targets the agglutinin-like sequence 3 protein Als3p, a cell wall antigen found on the surface of *Candida*. Both led to good antibody formation in animal tests as well as initial human studies, raising hopes for clinical efficacy in a manner similar to boostering.[18,146]

11.2. The significance of lactobacilli

The oral administration of probiotics containing specific lactobacillus strains[36,56,61,103] has produced encouraging, yet controversial, results which require further investigation. Lactobacillus strains have been identified which have fungicidal and immune-stimulating effects

in vitro[71] and have been found to significantly reduce vaginal colonisation *in vivo* after treatment of vulvovaginal candidosis in comparison with placebo.[72] Over a period of 6 months, monthly administration of lactobacilli for 6 days in conjunction with itraconazole 2× 200 mg for 1 day showed no improvement over itraconazole alone in the reduction of recurrence rates in chronic recurring vulvovaginal candidosis. Nonetheless, these treatment measures were found better than classical homoeopathy with a high degree of significance.[157]

11.3. Over-the-counter treatment?

Self-treatment (over-the-counter) of vulvovaginal candidosis using clotrimazole, and also fluconazole in several countries, is practiced meanwhile in more than 80% of cases. Although it was optimistically thought in the early 1990s that patients were almost always able to correctly diagnose vaginal candidosis themselves, this has meanwhile been proven to be incorrect (at least for now).[6,57,149] Only one-third of 95 women who purchased a vaginal antimycotic for self-treatment were found to have a *C. vaginitis*.[39] It is therefore being recommended again that treatment should only take place after a correct medical diagnosis has been made.

12. Future research

A number of gaps remain in our knowledge of *Candida*–host interactions and require further research. For example, How can *C. albicans* virulence factors be counteracted? How can the attachment of *Candida* cells to the vaginal epithelium be reduced? How can the defence mechanisms of the vagina be strengthened (e.g. T-lymphocyte stimulation, humoral factors, allergies)? Is it possible to vaccinate against *Candida*? Which new antimycotics are able to effectively treat *C. glabrata* and *C. krusei* intravaginally? How does *Candida* interact with vaginal flora, as it has been shown that abnormal bacterial flora of the vagina can penetrate the vaginal epithelium together with pseudohyphae, which is not normally the case in bacterial disorders of the vagina.[139] Why does clotrimazole treatment in early pregnancy reduce the number of premature births?

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Annex guideline report

1. Consensus procedure

The guideline was developed in participation with a representative group of professional users. Because it represents an update with relatively limited changes, a consensus meeting was not held. The changes were gathered using a written DELPHI procedure, summarised by the coordinator and then inserted. In a total of three rounds, this final version was unanimously adopted.

2. Patient participation

Patient representatives were not involved due to the lack of appropriate patient organisations.

3. Assessment and management of potential conflicts of interest

All contributors filled out the Association of the Scientific Medical Societies (AWMF) form. The majority of contributors reported financial relationships with companies. Conflicts of interest were not specifically examined. Formal, consensus-based working methods were used to prevent the distorted communication of results by the guideline working group.

4. Participation of professional societies/approval

This guideline was approved by the following professional societies and contributors:
German Society for Gynecology and Obstetrics (DGGG – Deutsche Gesellschaft für Gynäkologie und Geburtshilfe)
Working Group on Infections and Immunology in Gynecology and Obstetrics (AGII – Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Gynäkologie und Geburtshilfe)
German Dermatological Society (DDG – Deutsche Dermatologische Gesellschaft)
German Mycological Society (DmykG – Deutschsprachige Mykologische Gesellschaft)

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Dermatology

Prof. Dr. med. Jochen Brasch, University Hospital Schleswig-Holstein, Campus Kiel, DDG, DMykG (responsible).

Prof. Dr. med. Martin Schaller, University Hospital Tübingen, DDG, DMykG.

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Prof. Dr. med. Herbert Hof, Mannheim, DMykG.

Haemato-oncology

Prof. Dr. med. Oliver Cornely, University Hospital Cologne, DMykG.

Prof. Dr. med. Markus Ruhnke, Charité Berlin, DMykG.

5. Validity/updates

The validity of these guidelines was confirmed by the Executive Board of the DGGG and the DGGG Guidelines Commission in December 2013.

This guideline is valid until 12/2016.

If potentially relevant changes should occur in the meantime, these will be communicated to the working group by the coordinator and it will be decided whether a revision or addendum is necessary. Comments on the guideline are welcome.

Guideline Coordinator: Prof. W. Mendling.