Vulvovaginal Candidosis (excluding chronic mucocutaneous candidosis). Guideline of the German Society of Gynecology and Obstetrics (AWMF Registry No. 015/072, S2k Level, December 2013)

Die Vulvovaginalkandidose (außer chronisch mukokutaner Kandidose). Leitlinie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (AWMF-Registernummer 015/072, S2k-Level, Dezember 2013)

Authors W. Mendling[1], K. Friese[2], I. Mylonas[2], E.-R. Weissenbacher[3], J. Brasch[4], M. Schaller[5], P. Mayser[6], I. Effendy[7], G. Ginter-Hanselmayer[8], H. Hof[9], O. Cornely[10], M. Ruhnke[11]

Affiliations The affiliations are listed at the end of the article.

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Correspondence
Prof. Dr. med. Werner Mendling
Deutsches Zentrum für Infektionen in Gynäkologie und Geburtshilfe
St. Anna-Klinik
Vogelsangstraße 106
42109 Wuppertal
w.mendling@t-online.de

I. Guideline Information

Editor

Lead professional organization
German Society for Gynaecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe [DGGG] e. V.
Head Office of DGGG and Professional Societies
Hausvogteiplatz 12
10117 Berlin
Tel.: + 49 (0) 30-5 14 88 33 40
Fax: + 49 (0) 30-5 14 88 33 44
info@dggg.de
http://www.dggg.de/

President of the DGGG
Prof. Dr. med. Diethelm Wallwiener
Universitätsfrauenklinik Tübingen
Calwerstraße 7
72076 Tübingen

DGGG Guidelines Representative
Prof. Dr. Matthias W. Beckmann
Universitätsklinikum Erlangen-Nürnberg
Frauenklinik
Universitätsstraße 21–23
91054 Erlangen

DGGG Guidelines Secretariat
Dr. Paul Gaß, Tobias Brodkorb, Marion Gebhardt
Universitätsklinikum Erlangen-Nürnberg
Frauenklinik
Universitätsstraße 21–23
91054 Erlangen
Tel.: + 49 (0) 91 31-85/4 40 63
or + 49 (0) 91 31-85/3 35 07
Fax: + 49 (0) 91 31-85/3 39 51
fk-dggg-leitlinien@uk-erlangen.de
http://www.dggg.de/leitlinienstellungnahmen

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Guideline documents

The editorially complete, long version of these guidelines as well as a summary of the conflicts of interest of all the authors can be found on the homepage of AWMF: http://www.awmf.org/leitlinien/detail/ll/015-072.html

Authors

See **Table 1**.

Summary

The estrogenized vagina is colonized 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 defense mechanisms, gene polymorphisms, allergies, serum glucose levels, antibiotics, psycho-social stress and estrogens 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 Candida albicans-associated vaginitis.
Typical symptoms include premenstrual itching, burning, redness and odorless 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.

Table 1 Authors.

	DGGG Consortium (AG)/AWMF/non-AWMF Professional Societies/Organisation/Association
Gynecologists	
Prof. Dr. Werner Mendling	(responsible, leading) German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe DGGG) Working Group on Infections and Immunology in Gynecology and Obstetrics (Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Gynäkologie und Geburtshilfe AGII) German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)
Prof. Dr. Klaus Friese	German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe DGGG) Working Group on Infections and Immunology in Gynecology and Obstetrics (Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Gynäkologie und Geburtshilfe AGII)
Prof. Dr. Ioannis Mylonas	German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe DGGG) Working Group on Infections and Immunology in Gynecology and Obstetrics (Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Gynäkologie und Geburtshilfe AGII)
Prof. Dr. Ernst-Rainer Weissenbacher	German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe DGGG) Working Group on Infections and Immunology in Gynecology and Obstetrics (Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Gynäkologie und Geburtshilfe AGII)
Dermatologists	
Prof. Dr. Jochen Brasch	German Dermatological Society (Deutsche Dermatologische Gesellschaft DDG) German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG) (leading)
Prof. Dr. Martin Schaller	German Dermatological Society (Deutsche Dermatologische Gesellschaft DDG) German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)
Prof. Dr. Peter Mayser	German Dermatological Society (Deutsche Dermatologische Gesellschaft DDG) German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)
Prof. Dr. Isaak Effendy	German Dermatological Society (Deutsche Dermatologische Gesellschaft DDG) German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)
Prof. Dr. Gabriele Ginter-Hanselmayer	German Dermatological Society (Deutsche Dermatologische Gesellschaft DDG) German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)
Mikrobiologists	
Prof. Dr. Herbert Hof	German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)
Hemato-Oncologists	
Prof. Dr. Oliver Cornely	German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)
Prof. Dr. Markus Ruhnke	German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)

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-Candida 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. Candida glabrata is not sufficiently sensitive to the usual dosages of antimycotic agents approved for gynecological 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. 800 mg oral fluconazole per day for 2–3 weeks is therefore recommended in Germany. Due to the clinical persistence of Candida 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 Candida albicans does not play a significant role in the use of polyenes or azoles.

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 colonization of Candida in healthy women, vaginal administration of antimycotics is often recommended in the third trimester of pregnancy in Germany in order to reduce the rate of oral thrush and diaper dermatitis in healthy full-term newborns.

Chronic recurrent vulvovaginal candidosis (CRVVC) 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 three days in the first week and a dosage-reduced maintenance therapy with 200 mg once a month for one year when the patient is free of symptoms and fungal infection (**Fig. 2**). 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.

Methods

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 randomized and prospective controlled studies were left over [31,43,70,108,134,145]. There were only 3 metanalyses or Cochrane analyses [105,150,159] 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.

II. Use of the Guidelines

1 Introduction

Vulvovaginal candidosis is an infection of the estrogenized 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 is 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.

2 Summary of Recommendations

2.1 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 yeasts, 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 titers is not recommended.

2.2 Topical treatment of acute vulvovaginal candidosis can be performed for a period of one day to one week using polyene (nystatin), imidazoles or ciclopirox olamine using a number of different preparations such as vaginal tablets, suppositories or creams; oral triazoles (one-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 is 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 colonization, provided that immune suppression, concomitant disease or chronic recurring vulvovaginal candidosis are not present. See 9.2 for treatment of vaginal colonization during pregnancy.

2.3 Topical treatment of chronically recurring Candida albicans vulvovaginitis consists of supressive 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. [31] (**Fig. 2**).

2.4 The typical oral and vaginal treatments for Candida 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 9.7). In Germany, oral posaconazole is recommended in combination with local nystatin and/or ciclopirox olamine treatment, as well as micafungin [143].

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).

2.5 In Germany, antimycotic treatment of asymptomatic vaginal Candida colonization is recommended during the final 6 weeks of pregnancy in order to prevent vertical transmission to healthy, full-term newborns during vaginal birth. This can significantly reduce neonatal Candida infections attributable to maternal colonization, which normally appear in the 2nd to 4th weeks of life in more than 10% of healthy, full-term newborns (see also 9.2).

3 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 Candida glabrata and several other Candida species, which only appear as blastospores) indicates an infection [83,133].

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 defense mechanisms [8].

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

Non-Candida albicans species, particularly Candida 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 (**Fig. 1** and **Table 2** as an example for Berlin) but no evi-

Species	HIV-negative n = 383	100%		HIV-positive 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	p = 0.001	8	33.3
C. krusei	2	2.3		0	0
C. dubliniensis	1	1.1		0	0
C. parapsilosis	1	1.1		1	4.2
C. famata	1	1.1		0	0
C. magnoliae				1	4.2

Fig. 1 Candida colonization of the vagina in healthy women [81].

Table 2 Distribution of vaginal Candida species in HIV-negative colonized 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

dence for the increased occurrence of non-Candida albicans species in vaginal colonization. In a retrospective, four-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 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 to 2% of vaginal cultures [81,100] (**Table 3**).

Different genotypes of Candida albicans strains have been identified in asymptomatic women and in those with acute Candida vaginitis [68]. Identical Candida 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].

4 Virulence Factors of Candida albicans

The first step between colonization 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 to 11 [75] and enzymes which enable Candida albicans to survive in macrophages [66].

Bacteria and fungi can form biofilms in which they are highly organized 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, non-Candida biofilms were found in numerous vaginal tissue samples; the well-known phenomenon that Candida pseudohyphae penetrate vaginal tissue 8 to 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 hybridization (FISH) [139].

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

5 Genital Colonization

On account of the estrogenization of the vagina [29] and the estrogen receptors of Candida albicans [107,140], pre-menarchal girls and post-menopausal women are less frequently vaginally colonized and generally do not suffer from Candida vaginitis. It has also been confirmed in animal tests that vaginal candidosis can only occur in sterilized animals after the administration of estrogen. Healthy, pre-menopausal women who are not pregnant are vaginally colonized in approximately 20 to 30% of cases, at least 30% of pregnant women are colonized in the third trimester and at least 30% of immune-deficient women are found to be colonized to the extent that cultures are used for detection [81,98] (**Fig. 1** and **Table 2**). With PCR, the detection of a vaginal Candida colonization is at least 10% higher [152]. Vaginal colonization can vary individually from time to time. In a longitudinal cohort study with 1248 healthy, asymptomatic young women, 70% were colonized at least once over the course of one year, although only 4% were colonized at all visits which took place every three months. Recent sexual intercourse, the injection of medroxyprogesterone acetate (an ovulation inhibitor) and simultaneous colonization with lactobacillus and B streptococcus were identified as risk factors [6].

The partner's sperm can be colonized 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-colonized woman can also represent an allergic response to Candida antigens. It is not clear whether the colonization of the partner's genital tract or the oro-intestinal tract of both partners can play a role in chronic recurring Candida vaginitis [133].

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

6 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 normalized [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 Candida glabrata is less virulent, women with Type II diabetes mellitus are more frequently colonized than healthy women [67,109].

Vaginal Candida colonization is probably not increased by modern oral contraceptives with low estrogen 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 estrogen dosage [153].

Women with high estrogen levels, and particularly during pregnancy, more regularly experience vaginal Candida colonization. Women who are already vaginally colonized 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] emphasizes the likely underestimated role of sexual activity in the recurrence of vaginal candidosis, as re-infections 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] and a non-secretor pheneotype 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, tumor necrosis factor, interleukin-6) after stimulation with beta-glucan or Candida albicans. In contrast, phagocytosis and elimination of fungi was unaffected in these patients, which explains why a lack of Dectin-1 is not associated with fungal infections. Interestingly, symptoms appeared in the homozygotic daughters between 10–12 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 neutralize Candida in order to prevent the steps between asymptomatic colonization, attachment and infection. Vaginal microbiota also play 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 (colonizing 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) recognized. It was found 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 Candida vaginitis express heat shock proteins during symptom-free intervals, which can provoke similar immunological defense 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 colonization and disposition – candidosis is the infection of the infected – immune-suppressed individuals are particularly likely to develop candidosis. 75% of otherwise healthy women develop vulvovaginal candidosis at least once in their lives and many experience more than 4 episodes per year (chronic recurring vulvovaginal candidosis/CRVVC) [23,133]. In an internet questionnaire with 6000 women in 5 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.

7 Clinical Symptoms

Due to the influence of estrogen, pre-menopausal women normally suffer primarily from vaginal candidosis, which can extend to the vulva, while post-menopausal women typically suffer from vulvar and/or intercrural candidosis. Clinical symptoms typically appear prior to menstruation: the cell proliferation induced by estrogens and the cytolysis induced by progesterone releases glycogen, which can be metabolized 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 odor in contrast to bacterial vaginosis. The inner labia can be odematous, 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 [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 pre-pausal and peri-pausal period [42,55,76,132,138]. Candida krusei vaginitis [129], Candida parapsilosis vaginitis [97] and the rare Saccharomyces cerevisiae vaginitis [83,123,131] are generally similar to Candida glabrata vaginitis and are associated with only mild clinical symptoms.
Candida cervicitis is unknown.
In comparison to 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].

8 Diagnosis

The diagnosis of vaginal candidosis is always made using a combination of medical history, clinical symptoms and the detection of yeasts. 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 with 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.

8.1 Necessary diagnostics

Medical history, gynecological 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 to 80% of vaginal candidosis cases [90,133], although they are only microscopically visible during colonization 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 in order 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 Candida albicans and Candida glabrata. The patient typically suffers from a Candida albicans vaginitis while the generally resistant Candida glabrata remains in situ after treatment. It is generally only present as a colonization and need not be treated again in the absence of symptoms.
In vitro sensitivity testing is not necessary and at most only if non-Candida albicans species are found and the infection chronically recurs.

8.2 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 (for example due to intestinal colonization). Superficial vaginal candidosis does not cause increased antibody levels.

9 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].

9.1 Colonization

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

9.2 Colonization during pregnancy

Almost all healthy full-term newborns who are colonized with Candida albicans during vaginal birth will develop oral thrush and/or diaper dermatitis at some point in the first year of life, peaking in the 2nd to 4th weeks [10, 11].

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

In retrospective studies [24–26, 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-Candida 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 gynecological dosages of 150–300 mg/day is harmless throughout pregnancy. In a cohort of 7352 pregnancies, however, 7 incidences of Fallot tetralogy were found in association with the medically indicated cumulative administration of 150–6000 mg of flucanozole in the first trimester; in the control group of 968 236 pregnancies where no flucanozole was administered in the first trimester, a significantly lower incidence was reported [88].

9.3 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 are 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 one to two weeks and 75% at 4 to 6 weeks after treatment [22, 80, 95, 105, 134].

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-day 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 gynacological treatment since ca. 1995):
▶ Vaginal cream 10 mg/g: 50 mg daily for 6 days

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 one 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 colonized on the penis or in the sperm.

Vaginal candidosis occurs much more frequently in HIV-positive women (**Fig. 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.

9.4 Side effects

All vaginal and local antimycotics are well tolerated. Azoles and ciclopirox olamine can cause minor local burning in 1 to 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 (for example anaphylactic reactions, headaches, etc.).

9.5 Resistence to Candida albicans?

Although strains of vaginal Candida 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-Candida albicans species. Sensitivity testing should

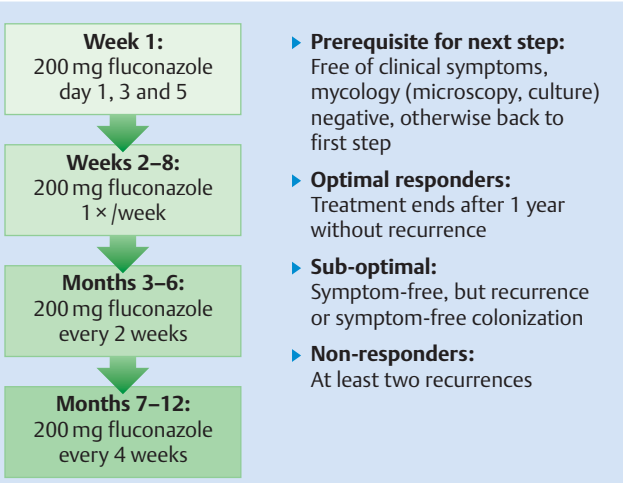

Fig. 2 Individualized, dose-reduced maintenance treatment with fluconazole in chronically recurring vulvovaginal candidosis (Donders et al. [31].

be performed in a laboratory experienced in mycology when a Candida albicans vulvovaginitis reappears after a longer period of chemoprophylaxis using fluconazole [127].

9.6 Non-Candida albicans vaginitis

Typical vaginal and oral treatments are generally unsuccessful against Candida 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 two 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 to 3 weeks against Candida glabrata vaginitis (but not colonization!) [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 echinochandin approved for the treatment of life-threatening mycoses, for example in hematooncology [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 flucytosin, however local clotrimazole, ciclopirox olamine [83,144] and (for example, 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].

9.7 Chronically recurring Candida albicans vulvovaginitis

Because infection requires colonization 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 whether local clotrimazole 500 mg, oral ketoconazole 100 mg or oral fluconazole 150 mg are administered, however recurrence occurs in approximately half of all patients shortly after ending treatment [130,134]. In a placebo-controlled study with a randomized collective of 387 women who received 150 mg fluconazole weekly for 6 months, the group of illness-free women after 12 months totaled 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. [31], which involves an initial dose of 3 × 200 mg fluconazole in the first week, followed by a dosage-reduced maintenance regimen (**Fig. 2**), 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 one year. The cumulative total dose amounted to 3800 mg fluconazole in 6 months and 5000 mg in one 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 one 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 Candida 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].

10 Open Questions

A number of questions remain open. How and why do immunological defense 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].

10.1 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 hyposensitization more than 30 years ago. In vitro studies using autologous membrane-bound Candida albicans antigens and T cells in a patient with chronic recurring Candida 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 hyposensitization. There has yet to be a therapeutic breakthrough in this field, despite numerous experiments to better understand the immunopathogenicity of Candida vaginitis [5, 7, 17, 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 in 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 Candida 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].

10.2 The significance of lactobacilli

The oral administration of probiotics containing specific lactobacillus strains [36, 56, 61, 103] have 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 colonization in vivo after treatment of vulvovaginal candidosis in comparison to placebo [72]. Over a period of six months, monthly administration of lactobacilli for six days in conjunction with itraconazole 2 × 200 mg for one 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 homeopathy with a high degree of significance [157].

10.3 Over-the-counter treatment?

Self-treatment ("over-the-counter" = OTC) 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 Candida vaginitis [39]. It is therefore being recommended again that treatment should only take place after a correct medical diagnosis has been made.

11 Future Research

A number of gaps remain in our knowledge of Candida-host interactions and require further research. For example: How can Candida albicans virulence factors be counteracted? How can the attachment of Candida cells to the vaginal epithelium be reduced? How can the defense mechanisms of the vagina be strengthened (for example T lymphocyte stimulation, humoral factors, allergies)? Is it possible to vaccinate against Candida? Which new antimycotics are able to effectively treat Candida glabrata and Candida 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?

Affiliations

[1] Deutsches Zentrum für Infektionen in Gynäkologie und Geburtshilfe, Wuppertal
[2] Klinikum der Universität München, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, München
[3] Premium Medizin, München
[4] Universitätsklinikum Kiel, Klinik für Dermatologie, Kiel
[5] Universitäts-Hautklinik Tübingen, Tübingen
[6] Universitätsklinikum Giessen, Klinik für Dermatologie, Venerologie und Allergologie, Giessen
[7] Klinikum Bielefeld, Hautklinik, Bielefeld
[8] Universitätsklinik für Dermatologie und Venerologie Graz, Graz, Österreich
[9] Labor Limbach, Heidelberg
[10] Uniklinik Köln, Klinik I für Innere Medizin, Köln
[11] Medizinische Klinik mit Schwerpunkt Onkologie und Hämatologie, Charité, Berlin

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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, summarized 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 organizations.

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 Immuology 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)

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.

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Participating medical professional societies and organisations	▸ German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe DGGG) e.V. (responsible) ▸ Working Group on Infections and Immunology in Gynecology and Obstetrics (Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Gynäkologie und Geburtshilfe AGII) ▸ German Dermatological Society (Deutsche Dermatologische Gesellschaft DDG) ▸ German Mycological Society (Deutschsprachige Mykologische Gesellschaft DMyKG)