mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Guideline

Guideline vulvovaginal candidosis (2010) of the german society for gynecology and obstetrics, the working group for infections and infectimmunology in gynecology and obstetrics, the german society of dermatology, the board of german dermatologists and the german speaking mycological society

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Abstract

Candida (C.) species colonize the estrogenized vagina in at least 20% of all women. This statistic rises to 30% in late pregnancy and in immunosuppressed patients. The most often occurring species is *Candida albicans.*

Host factors, especially local defense deficiencies, gene polymorphisms, allergic factors, serum glucose levels, antibiotics, psychosocial stress and estrogens influence the risk for a *Candida* vulvovaginitis. In less than 10% of all cases, non-albicans species, especially *C. glabrata*, but in rare cases also *Saccharomyces cerevisiae*, cause a vulvovaginitis, often with fewer clinical signs and symptoms.

Typical symptoms include premenstrual itching, burning, redness and non-odorous discharge. Although pruritus and inflammation of the vaginal introitus are typical symptoms, only less than 50% of women with genital pruritus suffer from a *Candida* vulvovaginitis.

Diagnostic tools are anamnesis, evaluation of clinical signs, the microscopic investigation of the vaginal fluid by phase contrast (400 x), vaginal pH-value and, in clinically and microscopically uncertain or in recurrent cases, yeast culture with species determination.

The success rate for treatment of acute vaginal candidosis is approximately 80%. Vaginal preparations containing polyenes, imidazoles and ciclopiroxolamine or oral triazoles, which are not allowed during pregnancy, are all equally effective. *C. glabrata* is resistant to the usual dosages of all local antimycotics. Therefore, vaginal boric acid suppositories or vaginal flucytosine are recommended, but not allowed or available in all countries. Therefore, high doses of 800 mg fluconazole/day for 2–3 weeks are recommended in Germany. Due to increasing resistence, oral posaconazole 2×400 mg/day plus local ciclopiroxolamine or nystatin for 15 days was discussed.

C. krusei is resistant to triazoles. Side effects, toxicity, embryotoxicity and allergy are not clinically important. A vaginal clotrimazole treatment in the first trimester of pregnancy has shown to reduce the rate of preterm births in two studies.

Resistance of *C. albicans* does not play a clinically important role in vulvovaginal candidosis.

Although it is not necessary to treat vaginal candida colonization in healthy women, it is recommended in the third trimester of pregnancy in Germany, because the rate of oral thrush and diaper dermatitis in mature healthy newborns, induced by the colonization during vaginal delivery, is significantly reduced through prophylaxis.

Chronic recurrent vulvovaginal candidosis requires a ''chronic recurrent'' suppression therapy, until immunological treatment becomes available. Weekly to monthly oral

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fluconazole regimes suppress relapses well, but cessation of therapy after 6 or 12 months leads to relapses in 50% of cases. Decreasing-dose maintenance regime of 200 mg fluconazole from an initial 3 times a week to once monthly (Donders 2008) leads to more acceptable results. Future studies should include candida autovaccination, antibodies against candida virulence factors and other immunological trials. Probiotics should also be considered in further studies.
Over the counter (OTC) treatment must be reduced.

1. Methods

A MedLine/PubMed research with the term ''vulvovaginal candidosis'' resulted in 2886 titles and limited to ''vulvovaginal candidosis therapy studies'' resulted in 237 reviews (2/2010). All were screened for title and abstract, but very few of the recent studies were randomized and/or conducted as prospective controlled trials (Fong 1992, Quereux et al. 2000, Upmalis et al. 2000, Lowe, Neal and Ryan-Wenger 2004, Sobel et al. 2004, Meyer, Göttlicher and Mendling 2006, Donders et al. 2008). There were 3 meta-analyses or Cochrane analyses (Pitsouni, Iavazzo and Falagas 2008, Watson et al. 2002, Young and Jewell 2001) and two guidelines (Mendling and Seebacher 2008, Bond et al. 2003). The rating in level of evidence and strength of recommendation was performed according to Abrams, Khoury and Grant (2007).

2. Definition

Vulvovaginal candidosis is an infection of the estrogenized vagina and the vestibulum, which can extend to the outside of the labia minora, the labia majora and the intercrural region. A candidosis of the cervix or the endometrium is not known. Connatal fetal candidosis and a candida amnionitis are rare events.

The terminus ''vulvovaginal candidosis'' or ''*Candida albicans* vulvovaginitis'' are recommended (Odds et al. 1992), The ending ''- iasis'' should be used for parasitic infections (e. g. trichomoniasis). (Loeffler 1983), but is also frequently used and accepted in the English language literature .

3. Summary of recommendations

3.1 The diagnosis of vulvovaginal candidosis is always a combination of clinical signs and symptoms and the presence of yeasts, which is usually performed by microscopic investigation (400fold phase contrast) of the vaginal fluid. In doubtful, in recurrent or in complicated cases a yeast culture with species determination is necessary. Serological blood tests are not recommended (Level of evidence (LoE) 1b, Grade of Recommendation (GoR) B).

3.2 Treatment of an acute vulvovaginal candidosis is possible with polyenes, imidazoles or ciclopiroxolamine in the form of vaginal tablets, suppositories or creams and with skin cream for the vulva, or with oral triazoles with a treatment duration of 1–6 days. All clinical and mycological treatment results are similar.

An asymptomatic colonization needs not to be treated, if there is no immunosuppression or chronic recurrent vulvovaginal candidosis. (LoE 1a, GoR A).

For treatment of vaginal colonization during pregnancy see 3.5.

3.3 Treatment of chronic recurrent *Candida albicans* vulvovaginitis involves – due to a lack of a causal immunological treatment – suppressive intermittent antimycotic treatment over a period of months with an oral triazole. The best results are obtained with the fluconazole regime described by Donders et al. (table 4) (LoE 2a, GoR B).

3.4 Common vaginal or oral treatments fail in *C. glabrata* vaginitis. Therefore, vaginal boric acid 600 mg capsules for 14 days, amphotericin B suppositories, vaginal 17% flucytosine or oral 800 mg fluconazole/day for 2–3 weeks are recommended (LoE 2a, GoR B). Posaconazole 2×400 mg/day in combination with local ciclopiroxolamine and/or nystatin for 15 days have been successfully used in Germany recently. *C. krusei* vaginitis is resistant to oral triazoles and should therefore be treated with local clotrimazole/imidazoles (or boric acid, which is not allowed in Germany) (LoE 2b, GoR B).

3.5 There is a German recommendation for local antimycotic treatment of vaginal *Candida* colonization during the last 6 weeks of pregnancy to inhibit vertical transmission to healthy, mature babies during vaginal

delivery. Neonatal *Candida* infection rates of more than 10% in the 2nd to the 4th weeks are shown to be significantly reduced (LoE 2a, GoR B).

4. Microbiology

Candida albicans is able to form blastospores, pseudomycelia, true mycelia and chlamydospores. *Candia glabrata* forms only blastospores.

Blastospores use usually formed in colonized women and together with (pseudo–) mycelia in vaginitis patients (Mendling 2006, Sobel 2007).

85–95% of the colonizing vaginal *Candida* species in premenopausal and pregnant asymptomatic and healthy women and in women with acute *Candida* vaginitis are *Candida albicans*, whereas non-albicans species, especially *C. glabrata*, are more frequent in postmenopausal, in diabetic and in immunosuppressed women (Odds 1988, Goswami et al. 2000, de Leon et al. 2002, Corsello et al. 2003, Paulitsch et al. 2006, Goswami et al. 2006, Mendling, Niemann, and Tintelnot 2007) (Tables 1 and 2). There are regional differences in the distribution of *Candida* species.

C. krusei, C. guilliermondii, C. tropicalis, C. parapsilosis and others can cause a vulvovaginitis with typical symptones (Spinillo et al. 1995, Singh et al. 2002, Nyirjesy et al. 2005, Mendling et al. 2007, Sobel 2007).

Saccharomyces cerevisiae is rarely able to cause vaginal symptoms (Sobel 1993, Mendling 2006), but is identified in about 1–2% of cultures (Mendling et al. 2007, Paulitsch et al. 2006) (Table 3).

Ranging between 80–95%, *Candida albicans* is also the most frequent yeast in chronically recurrent vulvovaginal candidosis, with small regional differences (Sobel 2007).

There is no evidence of an increase of non – *albicans* species in either acute or in recurrent vaginal candidosis, although this has been proven in intensive care and hematooncology and is thus often mentioned also in gynecology (Walker et al. 2000, Sobel et al. 2004, Donders et al. 2008).

There is evidence for different genotypes of *C. albicans* strains in asymptomatic women and in those with acute *Candida* vaginitis (Li et al. 2008).

Table 1 *Candida* colonization of the vagina in healthy women (Mendling et al. 2007).

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

5. Genital colonization

Due to estrogenization of the vagina (Dennerstein and Ellis 2007) and estrogen receptors of *C. albicans* (Powell 1984, Tarry et al. 2005) premenarchal girls and postmenopausal women are less frequently vaginally colonized and therefore do not usually suffer from *Candida* vaginitis. Approximately 20–30% of healthy, non pregnant and premenopausal women are vaginally colonized (by culture methods), while at least 30% of pregnant women in the third trimenon and immunodeficient women are colonized (Odds 1988, Mendling, Niemann and Tintelnot 2007) (Tables 1-2). Vaginal colonization can change individually over time, however: in a one year longitudinal cohort study with 1248 asymptomatic healthy young women, 70% had once been colonized, but only 4% of them were colonized at all visits, which took place every 3 months. Risk factors included recent sexual intercourse, injection of medroxyprogesteronacetate and concurrent colonization with lactobacilli and B-streptococci (Beigi et al. 2004).

The partner's sperm can also be colonized by the identical *Candida* strain found in the vagina (Mendling et al. 1998), although the partner is free of symptoms. *Candida* prostatits is a very rare event seen only in immunosuppressed men (Golz and Mendling 1991, Sobel, Fischer and Kauffman 2010). Nonetheless, the role of the partner's genital colonization or the orointestinal colonization of both partners as source of recurrence of recurrent *Candida* vaginitis is not clear (Sobel 2007).

The step from colonization to vaginitis is not well understood and appears to involve underlying host factors (Fidel 2005). As infection is colonization plus disposition, (''Candidosis is an illness of the ill''), especially immunosuppressed people develop candidoses. Nonetheless 75% of obviously healthy women develop a vaginal candidosis once in their lifetime, and probably up to 10% of them experience more than four episodes per year (chronic recurrent vulvovaginal candidosis/CRVVC) (Corsello et al. 2003, Sobel 2007).

6. *Candida* virulence factors

The first step from colonization to infection is the attachment of the *Candida* cell to the vaginal wall

Table 2 Distribution of vaginal *Candida* species in HIV-negative colonized women (Mendling et al. 2007).

Patients	Premenopausal		Postmenopausal		Pregnant		Not pregnant	
all patients with	*n* = 338		*n* = 45		*n* = 192		*n* = 146	
positive cultures	*n* = 82 (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 (Mendling et al. 2004).

	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. cereviciae)*	11	2.3

through mannoproteins (Sobel et al. 1981, Farrell, Hawkins and Ryder 1983, Thrumbore and Sobel 1986).

The most important virulence factors are probably the secreted aspartate proteinases (SAP 1–10) and proteases which are secreted especially from the top of germinating pseudomycelia (Rüchel, Fegeler and Trost 1982, de Bernardis et al. 1990, Naglik et al. 2004) and correlate with pathogenicity (Cassone et al. 1987, Ghannoum 2000).

Iron binding by host cells through siderophores (Ismail and Lupan 1986, Ghannoum and Abu-El Teen 1990), a strong pH-tolerance from 2 to 11 (Meinhof 1974) and enzymes, which enable *C. albicans* to survive in macrophages, are also important virulence factors (Lattif et al. 2006).

7. Predisposing host factors

As *Candida* strains and species differ in pathogenicity, candidosis develops due to the *Candida* strain and to weakened local defense mechanisms (de Bernardis et al. 2005).

An impaired tolerance for glucose was found in about 25% more women with CRVVC than in controls (Donders et al. 2002). Although C. glabrata is less ''virulent'', more women with type 2 diabetes are colonized than healthy women (de Leon et al. 2002, Ray et al. 2007), which underlines the importance of host factors.

Diabetic patients suffer more frequently from vaginal candidoses, and treatment fails, if the serum glucose levels are not normalized (Bohanna 1998).

Modern oral contraceptives with low estrogen levels, which do not significantly influence the carbohydrate metabolism (Gaspard et al. 2003), do not increase vaginal *Candida* colonization, (Davidson and Oates 1985) or the frequency of infection rates (Foxmann 1990). Some results do contradict this finding, however (Cetin et al. 2007).

Vaginal colonization rates are higher in women with a well estrogenized vagina, especially during pregnancy.

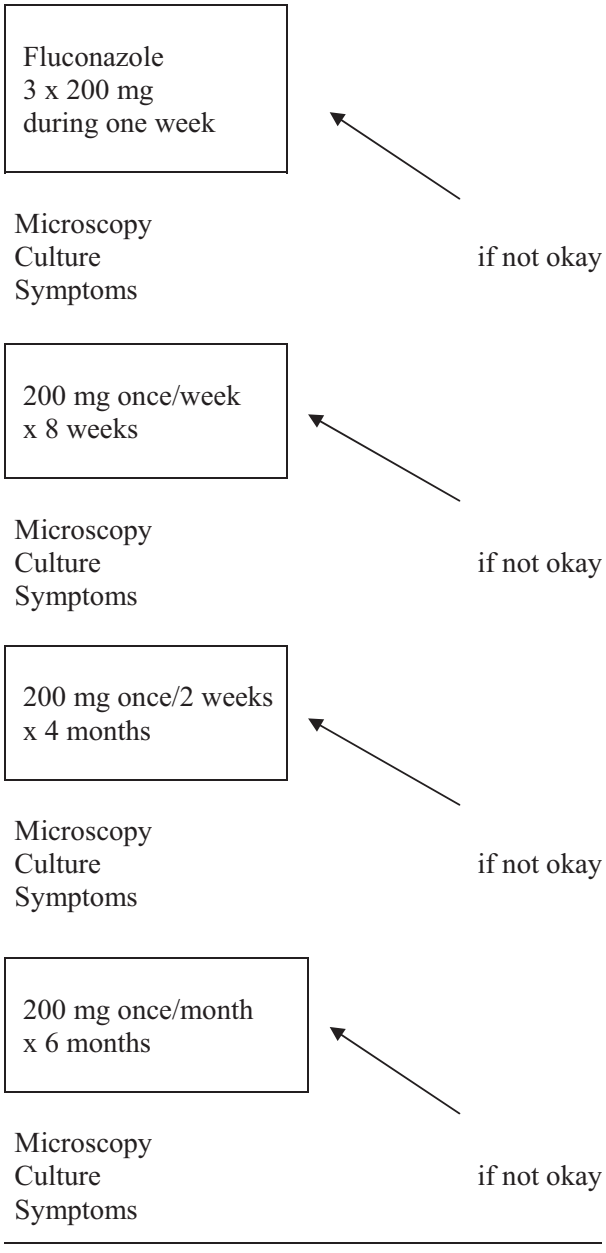
Women, who are already vaginally colonized by *Candida*, have up to a 33% risk of developing *Candida* vaginitis after antibiotic treatment (Eckert et al. 1998, Pirotta et al. 2003, Pirotta and Garland 2006, Xu et al. 2008).

Candida albicans can also form an adherent biofilm at the surface of intrauterine devices (Auler et al. 2010, Chassot et al. 2008).

Although vaginal candidosis often occurs in women with normal lactobacillus flora, lactobacilli have been found in lower numbers, when women have vaginal candidosis (Auger and Joly 1980). The potential protective role of lactobacilli or their special strains against yeast infections is not yet understood. Coexistence of bacterial vaginosis and vaginal candidosis is rare and occurs in about 5% of cases.

Sobel underlines the probably underestimated role of sexual behaviour for the recurrence of vaginal candidosis (Sobel 2007), suggested by repeated infections following sexual intercouse (Eckert et al. 1998, Reed et al. 2003).

Table 4 Individualized decreasing – dose maintencance fluconazole regime for recurrent *Candida albicans* vulvovaginitis (Donders et al. 2008).



Last but not least, genetic factors are responsible for recurrences since mannose-binding lectin gene polymorphisms (Babula et al. 2005, Donders, et al. 2008) and the blood group ABO-Lewis non-secretor phenotype (Chaim et al. 1997) have been identified as risk factors.

Women with atopic dermatitis more frequently develop vaginal candidosis (Neves et al. 2005) and allergic phenomena are found to be important for the development of the clinical symptoms, especially redness and itching (Witkin et al. 2000, Sobel 2007).

Women with a history of recurrent *Candida* vaginitis express immunologically important vaginal heat shock proteins in the symptom-free interval (Geraldo et al. 1999, Raska et al. 2008).

Psychosocial stress is also an important risk factor for Candida vulvovaginitis (Meyer et al. 2006, Ehrström et al. 2007), probably by causing immunosuppression. But vice versa recurrent vaginal candidoses have a significant negative impact on work and social life (Birkner et al. 2005, Nyijesy et al. 2006).

8. Clinical symptoms

Due to the estrogen-induced conditions, premenopausal women suffer primarily from vaginal candidosis which can extend to the vulva, while postmenopausal women only suffer from a vulva and/or intercrural candidosis.

The clinical symptoms typically occur premenstrually due to higher sugar levels in the vagina after the ovulation (Eckert et al. 1998).

In approximately 90%, pruritus is the most typical, but not reliable symptom, because only 35–40% of women with itching have a *Candida* vaginitis (Anderson, Klink and Cohrsson 2004, Mendling, Niemann, and Tintelnot 2007).

Discharge can vary from a thin fluid often at the beginning of an acute vaginal candidosis to cottage-cheese-like or no discharge at all (Spacek et al. 2005). From clinical and treatment aspects, the classification of vulvovaginal candidosis (Sobel 2007) is useful, although (pseudo-)hyphae, which are mentioned as a distinguishing factor, are not found in all cases of uncomplicated candidosis.

There is vaginal redness, soreness, burning, dyspareunia and dysuria. Symptoms alone do not allow patients or clinicians to confidently distinguish between causes of a vaginitis, but a lack of itching and inflammation makes vaginal candidosis less likely (Anderson, Klink and Cohrssen 2004). In contrast to bacterial vaginosis there is no unusual odour. The labia minora can be swollen, and burning fissures can occur especially in recurrent cases.

Dermatologists differentiate vesiculopustulous, eczematoid and follicular forms of vulvar candidosis (Mendling and Seebacher 2008).

An adherent white layer of discharge can be seen on the vaginal wall in serious cases, which can cause bleeding, if it is removed.

The rare *Candida glabrata* vaginitis, which usually occurs in the late pre- and the perimenopausal decades

(Mendling 1984, Sobel 1998, Spinillo et al. 1995, Fidel et al. 1999), *Candida krusei* vaginitis (Singh et a. 2002), *Candida* parapsilosis vaginitis (Nyirjesy et al. 2005), and, as a rare event, *Saccharomyces cerevisiae* vaginitis (Sobel 1993, Mendling 2006, Savini et al. 2008) are associated with mild clinical symptoms.

The cervix is not infected.

9. Diagnosis

The diagnosis of a vaginal candidosis always involves a combination of anamnesis, clinical signs and symptoms and the presence of yeasts.

9.1. Necessary/Obligate

Clinical anamnesis, gynaecological examination, pH measurement and microscopic investigation of the vaginal fluid with 10% potassium hydroxide or saline solution of the vaginal fluid (400fold phase contrast) are diagnostically essential. Budding cells or (pseudo-) hyphae can be detected in only 50–80% of patients with vaginal candidosis (Müller et al. 1981, Sobel 2007). The vaginal white blood cell count may be, but needs not be elevated. Unfortunately there is a lack of experience and teaching in many hospitals and private practices around the world (Donders 2001, Ledger et al. 2000, Mendling 2006).

If no blastospores or (pseudo-)hyphae are seen microscopically and in chronic recurrent or complicated cases, a species identification by culture is necessary (Nyirjesy et al. 1995, Eckert et al. 1998, Mendling 2006, Hoffstetter et al. 2008).

Routine cultures are not necessary, if yeasts are found microscopically.

The typical culture medium is Sabouraud agar, but there are other suitable media commercially available, for example Chrom Agar, Microstix – Candida and others.

It is possible, that two different *Candida* species will be cultured in one candida vaginitis, for example *C. albicans* and *C. glabrata*. The patient suffers in such a case from a *C. albicans* vaginitis. After treatment, *C. glabrata* (resistant!) remains *in situ*, only colonizing the vagina, and needs not be treated.

9.2. Ineffective

Serological tests are not useful for the diagnosis of vulvovaginal candidosis because low antibody levels can be found in most women with or without vaginal candidosis due to intestinal colonization and because this superficial vaginal disease does not cause significant antibody levels.

10. Therapy

There are many conventional and alternative therapies (Wilson 2005)

Polyenes form complexes with ergosterole of the yeast cell wall and thus change its permeability (Scheklakow et al. 1980).

Azoles inhibit the transformation of lanosterole to ergosterole in the yeast cell wall (Plempel 1980).

Ciclopiroxolamine inhibits probably important iron-dependent enzymes through chelate formation (Niewerth et al. 2003).

Patients often prefer oral treatment, if they are given a choice (Tooley 1985).

10.1. Colonization

Asymptomatic, vaginally colonized women do not require treatment, if they are immunocompetent and the candidosis is not chronically recurrent.

10.2 Colonization during pregnancy

Nearly all healthy, mature neonates, who were colonized by their mothers *Candida* during vaginal delivery, develop oral thrush and diaper dermatitis during their first year with a peak of 10–13% in the 2^{nd} to 4^{th} weeks of life (Blaschke – Hellmessen 1968, 1998).

In Germany prophylactic treatment of asymptomatic vaginal *Candida* colonization is recommended in the last weeks of pregnancy to protect the baby during vaginal delivery. This significantly reduces the risk of neonatal candidosis from more than 10% to only about 2% in the 4^{th} week of life (Schnell 1982, Blaschke-Hellmessen 1998, Mendling and Spitzbart 2008).

A retrospective randomized (Czeizel and Rockenbauer 1999, Czeizel, Fladung and Varga 2004, Hay and Czeizel 2007, Czeizel, Puko and Kazy 2007) and a prospective randomized (Kiss, Petricevic and Husslein 2004) study surprisingly showed a decrease in preterm deliveries after a vaginal treatment with clotrimazole in the first trimester, which requires further investigation.

10.3. Acute Candida vulvovaginitis

Acute vulvovaginal candidosis can be treated topically with polyenes (Nystatin, Amphotericin B or Pimaricin) or imidazoles (clotrimazole, miconazole nitrate, econaz-

ole nitrate, fenticonazole nitrate, sertaconazole nitrate, tioconazole nitrate, terconazole nitrate and others) (Mendling 1988, Sobel 2007), or with ciclopiroxolamine (Wajnberg and Wajnberg 1981).

Oral treatment with the imidazole ketoconazole (no longer typically used in Germany) or with the triazoles fluconazole or itraconazole or others is also possible.

There are vaginal suppositories or vaginal creams with dosages and formulations for treatment durations varying from one to three to six or seven days without toxicity (Ritter 1988).

All mycological and clinical success rates are equal and range between approximately 85% after 1 to 2 weeks and 75% after 4 to 6 weeks after the end of treatment (Cohen 1985, Mendling, Krauss and Fladung 2004, Sobel 2005, Nurbhai et al. 2007, Pitsouni et al. 2008).

Cure rates during pregnancy are significantly better with imidazoles than with polyenes (Young and Jewell 2000).

If the candidosis involves an area of the vulva outside the introitus or the inguinal region, the application of an antimycotic skin cream twice daily treatment for up to 6 days is recommended.

A ''blind'' treatment of the asymptomatic sexual partner is of no benefit for the patient (Buch and Skytte-Christensen 1982, Bisshop et al. 1986, Sobel 2007).

10.4. Side effects

All topically applied antimycotics are well tolerated, but topical azoles and ciclopiroxolamine can cause local burning in 1–10% of cases (Mendling 1988, Mendling, Krauss, and Fladung, 2004). Allergic reactions are possible, but rare.

The oral imidazole ketoconazole can cause side effects in about 5% of cases, for example headaches and non-viral hepatitis in 1 of 500000 to 1000000 gynecological patients (Cauwenberg 1984).

The hydrophilic fluconazole and the lipophilic itraconazole cause fewer side effects due to the inhibition of a yeast-selective cytochrome P_{450} – dependend enzyme, but like ketoconazole, however, they are not recommended during pregnancy.

10.5. Resistance of *Candida albicans*?

Although vaginal *Candida albicans* strains with higher minimum inhibitory concentrations (MIC) to fluconazole can be found (Richter et al. 2005), cases of azoleresistance are rare in gynecology (Mathema et al. 2001, Richter et al. 2005).

Clinical resistance does not correlate to laboratory MIC tests and vice versa, a well known problem in medical mycology.

Therefore, MIC – tests are usually not recommended (Sobel et al. 2003).

10.6. Non-*albicans* Vaginitis

Common vaginal and oral treatments usually fail in *Candida glabrata* vaginitis. Sobel et al. (2003) therefore recommend vaginal boric acid 600 mg capsules for 14 days, while Philips (2005) recommends amphotericin B suppositories. In particularly persistent cases a two week course of topical treatment with 17% flucytosine has been shown to be successful in 90% of cases (Sobel et al. 2003).

Boric acid is not allowed in Germany and other countries and vaginal flucytosine is not available there. High daily doses of 800 mg fluconazole for 2–3 weeks are therefore recommended in Germany according to resistance tests (Kunzelmann et al. 1996, Mendling and Seebacher 2008). There is an increasing failure rate associated with this treatment. Tietz (2009) therefore recommended oral posaconazole 2×400 mg/day within 30 minutes of a high fat meal in combination with local ciclopiroxolamine and/or nystatin for 15 days, which had been proven effective. Because this treatment regime is very expensive and is normally reserved for life - threatening mycoses, it is not accepted for other indications.

C. krusei vaginitis is resistant to fluconazole and flucytosine, but topical clotrimazole or other imidazoles or boric acid are mostly successful (Singh et al. 2002). Due to the rareness of cases, systematic studies are missing.

10.7. Chronically recurrent *C. albicans* vulvovaginitis

Since infection is colonization + disposition and no therapy against disposition (immunological local incompentence) exists, local or oral maintenance therapies to prevent relapses are recommended (Davidson and Mould 1978, Sobel 1985, Roth et al. 1990, Sobel et al. 2004).

Whether topical clotrimazole 500 mg, oral ketozonazole 100 mg or fluconazole 150 mg were given, the results were comparably effective, but recurrence occurs in half of the patients shorty after cessation of the therapy (Sobel 1985, Sobel et al. 2004). In a placebo - controlled trial involving 387 women randomly assigned to treatment groups receiving 150 mg fluconazole weekly for 6 months, the percentages of disease

free women after 12 months were 42.9% in the fluconazole group and 21.9% in the placebo group (Sobel et al. 2004).

Donders, Bellen et al. (2008) showed that an initial dose of 3 × 200 mg fluconazole in the first week followed by a decreasing dose maintenance regime (Table 4) in 117 women (without a placebo control group) achieved 90% disease free patiens after 6 months and 77% disease free patients after one year.

11. Open questions.

Many open questions nonetheless remain in regard to the treatment of *Candida* vaginitis. Why and how do immunological defense mechanisms allow acute and chronically recurrent candidosis or inflammation? Antimycotics are not the solution!

11.1. Immunological therapies?

Until now no proven immunotherapy for (chronically recurrent) vaginal candidoses has been shown to exist, although Rosedale and Brown (1978) reported encouraging initial results from hypersensitization over thirty years ago. The author's own *in vitro* studies with an autologous membrane bound *Candida albicans* antigen in a patient with chronically recurrent *Candida albicans* vaginitis showed improved immunological reactions in the patient's T lymphocytes as compared to results with commercially available *Candida* antigens (Koldovsky, Kariger and Mendling 1999). Meanwhile, Rigg, Miller and Metzger (1990) reported *Candida* allergen therapy and Moraes et al. (2000) and Rusch and Schwiertz (2006) reported first clinical results with *Candida* autovaccination. Antibodies against aspartyl-proteases, adhesins and allergens could potentially play a role in the future (Cassone, de Bernardis and Torososantucci 2005, Cassone 2009). Despite significant efforts to understand the immunopathogenesis of *Candida* vaginitis, a breakthrough still has not yet been made (de Bernardis et al. 1990, Mendling and Koldovsky 1996, Witkin, Geraldo and Linhares 2000, Fidel et al. 2004, Ip and Lan 2004, Babula et al. 2005, Birkner et al. 2005, Cassone, de Bernardis and Torososantuccii 2005, Fidel 2005, Neves et al. 2005, Raska et al. 2008, Wozniak et al. 2005, Weissenbacher et al. 2009).

11.2 Lactobacilli? Alternatives?

Intramuscular injection of not H2O2 – producing lactobacilli to induce antibodies (Birkner et al. 2005) and probiotics (Hilton et al. 1992, Jeavons 2003, Pirotta et al. 2004, Falagas, Betsi and Athanasiou 2005) have shown encouraging, but controversial results and require further investigation.

Watson and Calabretto (2007) complain the lack of randomized controlled trials for both conventional and non conventional management of recurrent vulvovaginal candidoses.

Meanwhile Lactobacilli strains have been identified, which have *in vitro* candidacidal and immunestimulating effects (Mailänder – Sanchez, Wagener and Schaller 2009, Martinez et al. 2009).

11.3 Over-the-counter (OTC-) therapy

OTC-therapy for vulvovaginal candidosis with clotrimazole or in some countries also with fluconazole represents meanwhile more than 80% of all treatment, although reports in the early 1990s optimistically suggested that patients might be able to successfully self-diagnose their *Candida* vaginitis have not proven correct (Walker et al. 2000, Beigi et al. 2004, Hoffstetter et al. 2004). Only 33% of a study group of 95 women, who purchased OTC vaginal antimycotics, were indeed found to have a *Candida* vaginitis (Ferris et al. 2002). Treatment with vaginal antimycotics should only be initiated after *Candida* vaginitis has been correctly diagnosed.

12. Future research

There are numerous gaps in our knowledge of *Candida* host reactions which require further research.

How can we, for example, act against *Candida albicans* virulence factors and how can we inhibit the adhesion of *Candida* cells to the vaginal epithelium? How can we improve the vagina's resistence to infections (T-lymphocyte stimulation, humoral factors, allergy)? Is a vaccination against *Candida* possible and successful? Which new antimicotics are able to satisfactory treat vaginal *C. glabrata* or *C. krusei* infections?

This guideline was consented in 2010 by the German Society of Gynecology and Obstetrics (DGGG), the Working Group for Infections and Infectimmunology in Gynecology and Obstetrics (AGII), the German Society of Dermatology (DDG), the Board of German Dermatologists (BDD) and the German-Speaking Mycological Society (DMykG), represented by an expert team of the following persons:

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Conflict of interests

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