Candida Species

Candida Vaginitis (CV)

- The incidence of Candida vaginitis (CV) is poorly documented, particularly since CV is not a reportable entity and is routinely diagnosed without laboratory testing, resulting in as much as 50% misdiagnosis (1).
- Candida vaginitis affects most females at least once during their lives, at an estimated rate of 70% to 75%, of whom 40% to 50% will experience a recurrence (3, 4).
- An estimated 75% of women will have at least one episode of vulvovaginal candidiasis (VVC) and 40% to 45% will have two or more episodes (20).
- Approximately 10% to 20% of women will have complicated VVC, requiring special diagnostic and therapeutic considerations (20).
- Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge; none of which are specific for VVC.
- Point-prevalence studies indicate that *Candida* species may be isolated from the lower genital tracts of approximately 20% of asymptomatic healthy women without abnormal vaginal discharge (6).
- Most studies indicate that CV is a frequent diagnosis among young women, affecting as many as 15% to 30% of symptomatic women visiting a clinician. Half of all college women will have experienced at least one episode of CV by the age of 25 (3).
- In the United States, CV is currently the second most common cause of vaginal infections, with bacterial vaginosis as the most common diagnostic entity (5).
- Most studies suggest a CV prevalence of 5% to 15%, depending on the population studied (2).
- Among women with symptoms of vulvovaginitis, 30% had yeast isolated, confirming the diagnosis of CV (7).

Vaginal *Candida* species

Between 85% to 90% of yeast strains isolated from the vagina belong to the *Candida albicans* species; other yeasts account for up to 15% of cases (8-10) (**Table 1**). *Candida tropicalis* is isolated from 1% to 5% of subjects and may be associated with a higher rate of recurrence after standard treatment (10, 11). *Candida glabrata* accounts for up to 10% of vaginal yeast isolates (8-10, 12). Symptomatic vaginitis caused by this organism is associated with less intense itching and dyspareunia (12) than caused by other *Candida* species, but the organism may be harder to eradicate with standard therapies (10, 13). The relative incidence of vaginitis caused by fungi other than *C. albicans* appears to be increasing, accounting for up to 18% of infections in some populations (10, 14). Non-albicans infections are associated with recurrent disease (21% versus 12% of initial infections) and with human immunodeficiency virus (21% versus 12% of infections in human immunodeficiency virus negative women), especially in those human immunodeficiency virus infected women who receive prophylaxes with imidazole or triazole (10). It is thought that the widespread use of topical antifungals, especially in short courses of treatment, may contribute to selection for non-*C. albicans* yeasts, which are less susceptible to these agents than *C. albicans*.

Table 1: ***Candida* species involved in vaginal fungal infections.**

Species	% of vaginal fungal infections
Candida albicans	91%
Candida glabrata	7%
Candida parapsilosis	1%
Candida tropicalis	1%

Pathogenesis

Using computer-assisted DNA-probe typing, Soli and co-workers (16) presented data to support the concept of “vaginal tropism”, in which Candida selected organisms demonstrate adaptation to unique anatomic niches that facilitate persistence and survival at certain anatomic sites, including the vagina.

Candida organisms are dimorphic, and may be found in humans during different phenotypic phases. In general, blastospores represent the phenotype responsible for transmission or spread of Candida, and are associated with asymptomatic colonization of the vagina. In contrast, germinated yeast producing mycelia most commonly constitute a tissue-invasive form of Candida, usually identified by the presence of symptomatic disease along with larger numbers of blastospores.

In order for *Candida* species to colonize the vagina, they must first adhere to vaginal epithelial cells. *Candida albicans* adheres to such cells in numbers significantly higher than those of *C. tropicalis*, *C. krusei*, and *C. kefyr* (17). This may explain the relative infrequency of the latter species causing vaginitis. All *C. albicans* strains appear to adhere equally well to exfoliated vaginal and buccal epithelial cells. In contrast, there is considerable person-to-person variation in vaginal epithelial cell receptivity to Candida organisms in adherence assays (16, 17).

High frequency, heritable switching occurs in the colony morphology of most *Candida* species. The variant phenotype switching enables *Candida* species to adapt to environmental factors such as drug challenges, and to escape the immune system. Although there is currently incomplete evidence that phenotypic switching occurs in vivo at 37°C, it is an attractive hypothesis for explaining spontaneous in vivo transformation from asymptomatic colonization to symptomatic vaginitis. Iron binding by Candida organisms has been shown to facilitate their virulence (18). The ready availability of erythrocytes and hemoglobin in the vagina creates an ideal niche for yeast possessing erythrocyte-binding surface receptors.

Candida organisms gain access to the vaginal lumen and secretions predominantly from the adjacent perianal area (19). The source of Candida infection for vaginal colonization may be initiated by the gastrointestinal tract, although this remains highly controversial (32). *Candida* species were recovered on rectal cultures from 100% of women with recurrent CV. Furthermore, the majority of Candida strains isolated from the rectum and the vagina are identical (32). However, women prone to recurrent CV are not known to suffer from perianal or rectal candidiasis. Two controlled studies using oral nystatin treatment, which reduces intestinal yeast carriage, failed to prevent symptomatic recurrence of CV (32-34).

Age appears to be an important factor in the overall incidence of vulvovaginal candidiasis which is seen predominantly in women of childbearing age. While the condition is extremely rare prior to menarche, the annual incidence increases dramatically toward the end of the second decade of life and peaks over the next two decades. Among college women, CV is more common among black than among white women (4) and is associated with the initiation of sexual activity (3).

High estrogen levels apparently favor overgrowth of yeasts, although such levels also promote the growth of lactobacilli (20-22). CV is more common in pregnancy and occurs in 10% of first trimester women and in 36% to 55% of women in their third trimesters (23). Symptomatic disease eventually developed in 60% to 90% of pregnant carriers, and old inoculation studies have confirmed the increased susceptibility of pregnant women (23). High levels of reproductive hormones provide an excellent carbon source for Candida organisms by producing a higher glycogen content in the vaginal tissue (24). A more complex mechanism is likely, in that estrogen enhances adherence of yeast cells to the vaginal mucosa. Several investigators demonstrated in vitro binding of female sex hormones to Candida organisms, as well as the capacity of certain hormones to enhance yeast mycelial formation and enhance virulence (25). Consequently, the rates of cured CV are significantly lower during pregnancy.

The onset of symptomatic CV is frequently observed during courses of systemic topical antibiotics. Broad-spectrum antibiotics, such as tetracycline and beta-lactams, are mainly responsible for exacerbation of symptoms (26). Vaginal colonization rates increase from approximately 10% to 30% (27). Antibiotics are thought to facilitate CV by eliminating the protective vaginal bacterial flora. Natural flora is thought to provide colonization resistance as well as to prevent germination and hence superficial mucosal invasion. In particular, aerobic and anaerobic resident lactobacilli have been pinpointed as providers of this protective function. Low numbers of lactobacilli in vaginal cultures were observed in women with symptomatic CV (28). The current concept of lactobacilli-yeast cell interaction includes competition for nutrients, and lactobacilli's steric interference of receptor sites on vaginal epithelial cells for Candida organisms (29).

The incidence of CV increases dramatically in the second decade of life, corresponding with the onset of sexual activity. It peaks in the third and fourth decades then declines in females older than 40 years. Penile colonization with Candida organisms is present in approximately 20% of male partners of women with recurrent CV (30, 31). Asymptomatic male genital colonization with *Candida* species is four times more common in male sexual partners of infected women and infected partners usually carry identical strains (15, 30). Sexual transmission of CV occurs during vaginal intercourse, although the relative role of sexual and nonsexual practices in introducing CV into the lower genital region has not been apprised (15, 30, 31).

Clinical significance

Acute pruritus and vaginal discharge are the usual presenting complaints, but neither symptom is specific to CV and neither is invariably associated with disease. The most frequent symptom is that of vulvar pruritus. Vaginal discharge is frequently minimal. Although described as typically cottage cheese-like in character, the discharge may vary from watery to homogeneously thick. Vaginal soreness, irritation, vulvar burning, dyspareunia, and external dysurea are commonly present. Odor, if present, is minimal and nonoffensive. Examination frequently reveals erythema and swelling of the labia and vulva, often with discrete pustulopapular peripheral lesions and fissure formation. Certain predisposing factors associated with increased yeast growth include glycosuria, diabetes mellitus, pregnancy, obesity, and recurrent use of antibiotics, steroids or immunosuppressive agents.

In men, Candida infection is expressed as a transient rash, erythema, and pruritus or a burning sensation of the penis that develops minutes after unprotected intercourse. The symptoms are self limited and frequently disappear after showering.

Diagnosis

The lack of specificity of symptoms and signs of CV precludes a diagnosis that is based soley on history and physical examination. Clinical signs and symptoms alone also should not be regarded as a satisfactory basis for diagnosis. Regrettably, both approaches are common in practice, as a myriad of infections and noninfections may cause patients to present identical signs and symptoms, hence the need for laboratory confirmation. The most specific symptom in genital Candida infection is pruritus without discharge, and even this criterion correctly predicted CV in only 38% of patients (43).

At present, laboratory identification of *Candida* species requires culturing and other microscopic preparation techniques, which are time-consuming and have an inherent weakness in that they may not be species-specific. Further complicating traditional analysis is the increasing number of auxotrophs that do not grow on the media required to perform the tests (44). Diagnosis of *C. glabrata* vaginitis is more difficult than that of typical Candida vaginitis because of the failure of this organism to form pseudohyphae and hyphea *in vivo*. Accordingly, on saline and KOH microscopy, numerous budding yeasts are seen, but hypha elements are absent. There is some evidence that vaginitis with *C. glabrata* often occurs at a somewhat higher vaginal pH, usually at the upper limit of normal. Not infrequently, *C. glabrata* vaginitis coexists with bacterial vaginosis, and the higher pH of the latter may represent the link between the two entities.

Current laboratory techniques for the identification of CV include:

- The 10% KOH preparation, with just 65% to 85% sensitivity.
- Direct microscopy. Several studies have consistently revealed that as many as 50% of patients with culture positive symptomatic CV (responding to antimycotic therapy) will have negative microscopy (19).
- The Papanicolaou (Pap) smear, which is unreliable as a diagnostic modality, showing a positive result in only 25% of cases.

- Candida cultures and the use of conventional morphological and metabolic characteristics. These are time-consuming and require several days for test results.

In order to decrease turn-around time, laboratory methods were devised for the rapid diagnosis of fungal infections which include detection of antibody (45), and cell wall mannan (46). Efforts have been directed toward molecular testing such as the use of rRNA genes for species identification.

The recent advent of Real-Time PCR technology allows for the detection of PCR amplification while the reaction is proceeding. Conventional PCR methods only allow the visualization of product at the end of the reaction, or end-point analysis. In addition to the highly specific primers that are used in a PCR reaction, Real-Time PCR utilizes a probe to enhance the sensitivity and specificity of the assay.

Recommendations

After conventional antifungal therapy for CV, resultant negative vaginal Candida cultures once more turn positive within 30 days in 20% to 25% of women, strongly supporting the hypothesis that yeast persistence and vaginal relapse is responsible for recurrent CV (2). Strains isolated before and after therapy are of identical types in more than two-thirds of recurrences (15). Symptomatic relief after clinically successful topical therapy for symptomatic vaginitis is accompanied by a drastic reduction in the number of viable yeast cells in the vagina. Small numbers of the microorganisms persist, however, within the vaginal lumen, generally in numbers too small to be detected by conventional vaginal culture (35).

It is also possible that a small number of Candida organisms might reside temporarily within the superficial cervical or vaginal epithelial cells, only to reemerge some weeks or months later. *C. glabrata* is more resistant to fluconazole than *C. albicans*. The MIC of fluconazole for *C. glabrata* is 16 μg/ml, which is much higher than for *C. albicans* (0.25 μg/ml), *C. tropicalis* (1 μg/ml), and *C. parapsilosis* (1 μg/ml) (36). Therefore, earlier information regarding the species causing CV may help physicians to select appropriate antifungal agents and regimens to treat patients.

The specific mechanisms of antifungal resistance to the azole class of antifungal agents are not yet fully understood. However, it has been suggested that the sterol composition of the fungal plasma membrane is altered, reducing the uptake of the antifungal agent into the cell. Recent studies with several different azoles evaluating *C. albicans*, *C. glabrata* and *S. cerevisiae* have demonstrated at least three known mechanisms of resistance including changes in the P-450 lanosterol demethylase enzyme, changes in the △5-6-sterol desaturase and an energy-dependent drug efflux mechanism (37-40). In *C. glabrata*, several mechanisms of azole resistance have been identified including increased P-450-dependent ergosterol synthesis and an energy dependent efflux pump of fluconazole, possibly via a multidrug resistance-type transporter (41, 42).

Treatment Guidelines

The Centers for Disease Control and Prevention (CDC) recommendations for the treatment and management of patients as outlined below, can be found in the Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) 2015 edition Sexually Transmitted Diseases, Treatment Guidelines. MMWR 64:72-75 (20).

Short-course topical formulations (i.e., single dose and regimens of 1–3 days) effectively treat uncomplicated vulvovaginal candidiasis VVC. The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80%–90% of patients who complete therapy.

Table 2. Treatment Recommendations. CDC's 2015 Sexually Transmitted Diseases Summary of 2015 CDC Treatment Guidelines Pocket Guide (20).

Recommended Regimens
Over-the-Counter Intravaginal Agents:
Clotrimazole 1% cream 5 g intravaginally for 7–14 days ***OR***
Clotrimazole 2% cream 5 g intravaginally for 3 days ***OR***
Miconazole 2% cream 5 g intravaginally for 7 days ***OR***
Miconazole 4% cream 5 g intravaginally for 3 days ***OR***
Miconazole 100 mg vaginal suppository, one suppository for 7 days ***OR***
Miconazole 200 mg vaginal suppository, one suppository for 3 days ***OR***
Miconazole 1,200 mg vaginal suppository, one suppository for 1 day ***OR***
Tioconazole 6.5% ointment 5 g intravaginally in single application
Prescription Intravaginal Agents:
Butoconazole 2% cream (single dose bioadhesive product), 5 g intravaginally in a single application ***OR***
Terconazole 0.4% cream 5 g intravaginally for 7 days ***OR***
Terconazole 0.8% cream 5 g intravaginally for 3 days
Terconazole 80 mg vaginal suppository, one suppository daily for 3 days
Oral Agents:
Fluconazole 150 mg orally in a single dose

**** The creams and suppositories in this regimen are oil-based and might weaken latex condoms and diaphragms. Patients and providers should refer to condom product labeling for further information.***

Special Considerations

Recurrent Vulvovaginal Candidiasis (RVVC): RVVC, usually defined as four or more episodes of symptomatic VVC in 1 year, affects a small percentage of women (<5%). *C. glabrata* and other non-*albicans Candida* species are observed in 10%–20% of patients with RVVC. Conventional antimycotic therapies are not as effective against these species as against *C. albicans.*

RVVC Treatment: Some specialists recommend a longer duration of initial therapy (e.g., 7–14 days of topical therapy or a 100 mg, 150 mg, or 200 mg oral dose of fluconazole every third day for a total of 3 doses (day 1, 4, and 7) to attempt mycologic remission before initiating a maintenance antifungal regimen.

Maintenance Regimens: Oral fluconazole (i.e., 100 mg, 150 mg or 200 mg dose) weekly for 6 months is the first line maintenance regimen. If this regimen is not feasible, topical treatments used intermittently can also be considered. Suppressive maintenance therapies are effective in reducing RVVC. However, 30%–50% of women will have recurrent disease after maintenance therapy is discontinued. Symptomatic women who remain culture positive despite maintenance therapy should be managed in consultation with a specialist.

Table 3: **Susceptibility of *Candida* species to antifungal drugs**. Modified from Pappas, *et al* (79).

	Fluconazole	Itraconazole	Voriconazole (not standardized)	Amphoteracin B	Caspofungin
Candida albicans	S	S	S	S	S
Candida tropicalis	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S (to I?)
Candida glabrata	S-DD to R	S-DD to R	S to I	S to I	S
Candida krusei	R	S-DD to R	S to I	S to I	S
Candida lusitaniae	S	S	S	S to R	S

S=Susceptible **S-DD**=Susceptible dose-dependant **I**=Intermediate **R**=Resistant

Severe VVC: Severe vulvovaginitis (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. Either 7–14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.

Non-*albicans* VVC: Options include longer duration of therapy (7–14 days) with a nonfluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for 2 weeks. If symptoms recur, referral to a specialist is advised.

Pregnancy: VVC frequently occurs during pregnancy. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women.

Compromised Host: Women with underlying immunodeficiency, those with poorly controlled diabetes or other immunocompromising conditions (e.g., HIV), and those receiving immunosuppression therapy (e.g., corticosteroid treatment) do not respond as well to short-term therapies. Efforts to correct modifiable conditions should be made, and more prolonged (i.e., 7–14 days) conventional treatment is necessary.

Other *Candida* Species

The genus Candida includes approximately 200 species. Among these, eight are most frequently isolated in human infections. While *Candida albicans* is the most abundant and significant species, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida kefyr*, *Candida krusei*, *Candida dubliniensis* and *Candida lusitaniae* are also isolated as causative agents of candidiasis infections **(Table 4)**. The variety of non-albicans *Candida* species involved in human pathology, their rising contribution to invasive infections and the unusual antifungal susceptibility profiles of some of these species makes their identification at the species level essential for epidemiological investigations and for optimizing therapy and patient management.

Table 4. *Candida* species commonly causing Candidiasis.

Species	Frequency
Candida albicans	50%
Candida glabrata	15% - 30%
Candida parapsilosis	15% - 30%
Candida tropicalis	15% - 30%
Candida krusei	~2%
Candida dubliniensis	~1%
Candida kefyr	~1%
Candida lusitaniae	~1%

Candida dubliniensis

Candida dubliniensis was first described as a novel species in 1995. This organism is very closely related to the important human yeast pathogen, *Candida albicans*. However, despite the very close phylogenetic relationship between *C. albicans* and *C. dubliniensis* and the fact that they share a large number of phenotypic traits, epidemiological and virulence model data indicate that they differ in pathogenicity and pharmacology. *C. dubliniensis* has been implicated as an agent of oral candidiasis in HIV-positive persons but has also been recovered from HIV-negative persons with clinical signs of oral candidiasis and from the genital tract of some women with vaginitis (48-50). The majority of *C. dubliniensis* clinical isolates tested to date are susceptible to fluconazole (MIC range, 0.125 to 1.0 g/ml) and to other commonly used antifungal drugs including ketoconazole, itraconazole and amphotericin B (51). It has been suggested that the ability of *C. dubliniensis* to rapidly develop resistance to fluconazole may contribute to its ability to successfully colonize the oral cavities of HIV-infected individuals who are receiving long-term therapy with this compound (52).

Molecular mechanisms of azole resistance in *C. dubliniensis* include increased drug efflux, modifications of the target enzyme and alterations in the ergosterol biosynthetic pathway (53). Its potential to cause deep or disseminated candidiasis is not known, largely because *C. dubliniensis* has rarely been isolated from sterile body sites (54); however, the phenotypic characteristics the organism shares with *C. albicans,* such as producing germ tubes and chlamydospores, suggest that some *C. dubliniensis* isolates may have been misidentified as *C. albicans*. The discrimination of *Candida albicans* from *Candida dubliniensis* is difficult to establish by classic biochemical methods, as these two species have almost identical phenotypes; yet, both species can be differentiated by their genetic profiles by the Real-Time PCR assay.

Candida krusei

Candida krusei is an opportunistic pathogen commonly implicated in urinary tract infections in immunocompromised patients and has emerged as a true, albeit uncommon, cause of fungal vaginitis (55, 56). Infections with *Candida krusei* have increased in recent years as a consequence of its intrinsic resistance to fluconazole, an antifungal azole widely used in immunocompromised individuals to suppress infections due to azole-susceptible *C. albicans*. *C. krusei* is predominately seen as a cause of vaginitis in comparatively older women. A possible pathophysiological explanation for the selection of *C. krusei* is that the older population may have been exposed to repeated episodes of vulvovaginal candidiasis and thus had been exposed to many courses of a wide array of antifungal therapy. The repeated exposure to azole-based antifungals, including topical agents, may cause a shift in the vaginal mycoflora from the more drug-susceptible *C. albicans* to the less drug-susceptible *Candida* species, such as *C. krusei* (47, 58).

Table 5: ***Candida albicans* and *Candida krusei* susceptibilities to various antifungal drugs**. Adapted with modification Singh *et al*, (56).

	C. albicans (n = 20)			*C. krusei* (n = 26)		
Antifungal Agent	**MIC range, µg / mL**	**MIC_{50} µg / mL**	**MIC_{90} µg / mL**	**MIC range, µg / mL**	**MIC_{50} µg / mL**	**MIC_{90} µg / mL**
Clotrimazole	0.006 – 0.50	0.010	0.06	0.030 – 0.50	0.125	0.25
Capsofungen	0.050 – 1.00	0.250	0.50	0.060 – 2.00	0.500	1.00
Fluconazole	0.130 – 8.00	0.130	2.00	32 - <64	32	>64
Itraconazole	0.0160 – 0.25	0.016	0.13	0.25 – 2.00	0.500	1.00
Voriconazole	0.006 – 0.13	0.030	0.03	0.25 – 1.00	0.250	1.00
Miconazole	0.010 – 0.13	0.013	0.03	1.00 – 4.00	2.000	4.00
Amphotericin B	0.030 – 0.50	0.120	0.25	0.25 – 1.00	1.000	1.00

Note: *C. albicans* isolates were recovered from women who experienced recurrent vaginal candidiasis.

Since cultures are rarely performed, there is limited data regarding the antifungal susceptibility of yeast causing vulvovaginal candidiasis. In a study by Singh *et al*., susceptibility testing was performed on vaginal yeast isolates from 593 patients with suspected vulvovaginal candidiasis **(Table 5)**. Among 84 patients with recurrent episodes, non-*albicans* species were detected more frequently (42% versus 20%) and treatment is further complicated by the fact that azole agents are less effective against these species (57).

In patients with chronic and recurrent fungal vaginitis, it should never be assumed that the yeast species responsible is invariably *C. albicans.* Signs and symptoms of vaginitis due to *C. krusei* appear to be indistinguishable from those of vaginitis due to other *Candida* species, an observation that emphasizes the need to obtain subspeciation of Candida prior to the initiation of antifungal therapy.

Prolonged, not abbreviated, therapy with either topical boric acid or topical clotrimazole or oral therapy with either ketoconazole or itraconazole should be considered as the first line therapy for patients with *C. krusei* vaginitis. Therapy with all active antifungal agents should also be prolonged (duration, usually 2 to 6 weeks), regardless of the agent used (56) **(Table 4)**.

Candida lusitaniae

Among the non-*albicans* species, *Candida lusitaniae* is of special interest owing to its uncommon susceptibility pattern (59-61). Rapidly acquired resistance to amphotericin B has been described or suspected, and some strains of *C. lusitaniae* may be intrinsically resistant (62, 63); therefore, the detection of amphotericin B resistance is essential for treatment of *C. lusitaniae*-associated infections (64).

The yeast *Candida lusitaniae* was first described by van Uden and by Carmo-Sousa as a common organism in the gastrointestinal tracts of warm-blooded animals (65). *C. lusitaniae* was found as a part of the mycoflora of the upper-respiratory, gastrointestinal and urinary tracts of hospitalized patients. This yeast species was recovered from both the skin and vagina of only one patient. Although an infrequent isolate overall (0.64% of 9,105 yeast isolates) (66), lately it has been recovered from a variety of clinical specimens including urinary tract infection and from vaginal candidiasis patients (67, 68).

In a study by Favel *et al*., the antifungal susceptibility of thirty-five *Candida lusitaniae* isolates was determined in vitro by the National Committee for Clinical Laboratory Standards (NCCLS) M27-P macrodilution methodology. All the isolates were susceptible to ketoconazole, itraconazole and fluconazole. Of the thirty-five isolates, eight (23%) were resistant to flucytosine. For amphotericin B, M27-P yielded a narrow range of MICs (0.06-0.5 mg/L) (**Table 6**) (69).

Table 6: **Antifungal susceptibility of *C. lusitaniae*.** Adapted with modification from Favel *et al*, (67).

Antifungal Agent	MIC_{50} (µg/L)	MIC_{90} (µg/L)
Amphotericin B	0.25	0.5
Flucytosine	0.06	> = 64
Econazole	0.12	0.12
Ketoconazole	0.03	0.06
Fluconazole	1	2
Itraconazole	0.12	0.5

Amphotericin B is the drug of choice for many systemic fungal infections (28). Amphotericin B susceptibility testing was recently performed and reported on 4,936 isolates of *Candida* species by the Etest methodology (70) (**Table 7**).

Table 7: **Comparative amphotericin B susceptibility testing results for 4,935 isolates of *Candida* species**. Adapted and modified from Pfaller MA, *et al*., 2004 (77).

Species	No. of isolates	MIC_{50} [a] (µg/L)	MIC_{90} [a] (µg/L)
Candida albicans	2,728	0.5	0.5
Candida glabrata	722	1	2
Candida parapsilosis	666	1	2
Candida tropicalis	528	1	2
Candida krusei	143	4	8
Candida lusitaniae	54	0.25	1
Candida species[b]	95	0.5	2
All Candida	4,936	0.5	2

[a] 50% and 90%, MICs at which 50% and 90% of isolates tested, respectively, are inhibited.
[b] Includes *C. guilliermondii* (39 isolates), *C. pelliculosa* (17 isolates), *C. kefyr* (15 isolates), *C. rugosa* (11 isolates), *C. dubliniensis* (5 isolates), *C. zeylanoides* (4 isolates), *C. lipolytica* (3 isolates) and *C. famata* (1 isolate).

Candida utilis

This organism adds to the growing list of *Candida* species

associated with human disease. *Candida utilis* was cultured from the blood of a patient with acquired immunodeficiency syndrome. The candidemia was apparently associated with catheter implantation. A report by Hazen KC, *et al.* describes the first demonstration and isolation of the industrially important yeast *C. utilis* from a urinary tract infection. In this present case, the organism was associated with chronic, symptomatic disease (72). In addition, *C. utilis* was also associated with fungal keratitis. The clinical features exhibited typical feather-like infiltration at the ulceration margin in this case. After treatment with topical fluconazole and amphotericin-B, the ulceration healed within 3 weeks (72).

Candida kefyr

Identified in 1931 and originally classified as *Endomyces pseudotropicalis*, *Candida kefyr* was considered a rarely isolated species that occasionally caused disease within immunocompromised individuals (73). Since then the organism has been reclassified several times and, most recently, has been deemed an emerging pathogen (74). Despite the limited literature documentation on *C. kefyr*, eight clinical studies and two case reports have established this organisms' ability to cause disease in humans (74). Though still a relatively rare cause of Candidiasis and fungemia, *Candida kefyr* has been isolated from a variety of body regions, including blood, urine, the esophagus and the cervical-vaginal tract in populations other than the immunocompromised (75, 76). Geographical distribution studies of clinically relevant Candida strains demonstrates a relatively low prevalence rate within the United States (~0.5%) with higher rates reported within Europe (**Table 8**). Resistance of *C. kefyr* isolates has been observed in conjunction with amphotericin B therapy (77) and building resistance to common antifungal agents (77, 78) (**Table 9**).

Diagnosis

Traditional diagnosis of Candida infections is slow and complicated. The ability to diagnose and identify candidiasis may be enhanced by the use of molecular techniques, such as Polymerase Chain Reaction (PCR).

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Table 8: Geographical distribution of infectious *Candida* species. Adapted with modification from Pfaller MA *et al,* 2006 (78).

	% of isolates					
***Candida* species**	**Asia (514)**	**Latin America (548)**	**Europe (847)**	**Canada (156)**	**United States (587)**	**Total (2,656)**
Candida albicans	60.2	48.9	63.5	64.1	44	55.6
Candida glabrata	7.3	4.2	11.8	21.8	27.4	13.4
Candida kefyr	0.2	0.4	1.3	0.0	0.5	0.6
Candida krusei	0.8	1.8	4.1	1.3	2.0	2.4
Candida lusitaniae	1.0	0.5	0.4	0.6	2.0	0.9
Candida parapsilosis	16.2	19.7	10.6	9.0	14.8	14.4
Candida tropicalis	12.5	16.4	7.6	2.6	7.8	10.1

Table 9: Susceptibility of *Candida kefyr* to common antifungal agents. Compiled with modification from Pfaller, MA *et al*., 2006 and Pfaller, MA *et al*., 2004 (88, 89)

		Cumulative % susceptible at MIC (µg/mL) values of:						
Antifungal Agent	**No. of isolates**	**0.007**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**
Fluconazole	29	0	10	55	93	100	100	100
Ravuconazole	29	100	0	0	0	0	0	0
Flucytosine	29	31	66	66	72	90	90	100
Micafungin	17	0	0	41	100	0	0	0
Capsofungin	17	12	94	100	0	0	0	0

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MDL#: 5362586 ***Test Results** **Physician Copy**

Patient Information:	**SSN:** XXX-XX-1111 **DOB:** 1/1/1987 (Age:27)	**Ordering Physician/Lab:**	**NPI:** 1234567890
DOE, JANE 56 LIBERTY DRIVE DAYTON, NJ 08810		**JOHN DOE, MD** 202 ANY STREET DAYTON, NJ 08810 **Tel: 555-555-5551** **Fax: 555-555-5555**	

Patient ID: Date Processed: **10/1/2015** Date Reported: **10/3/2015**

Test	Specimen	Date Collected / Comment	Results: Normal	Results: Abnormal	Reference/Units/Comments
Candida albicans by Real-Time PCR *	*Swab - 1*	9/29/2015 Vaginal	**Negative**		
551 Verified 10/1/2015					
Candida tropicalis by Real-Time PCR *	*Swab - 1*	9/29/2015 Vaginal	**Negative**		
557 Verified 10/1/2015					
Candida parapsilosis by Real-Time PCR *	*Swab - 1*	9/29/2015 Vaginal	**Negative**		
558 Verified 10/1/2015					
Candida glabrata by Real-Time PCR *	*Swab - 1*	9/29/2015 Vaginal		**Positive**	
559 Verified 10/1/2015					
Candida glabrata fluconazole resistance by X-Plate Technology *	*Swab - 1*	9/29/2015 Vaginal		**Resistant**	**Candida glabrata isolated; Fluconazole Resistant.**
582 Verified 10/3/2015					

*This test was developed and its performance characteristics determined by Medical Diagnostic Laboratories, L.L.C. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

A positive result is provided for bacteria, virus, and/or fungal species when PCR amplification (real-time PCR), sequence information (Pyrosequencing), and/or sequencing analysis occurs above cut-off levels established by the laboratory. Pertinent reference intervals for the tests reported above are available from the laboratory upon request.

end of report

View: M

Mail:	Yes	Overnight
	All	Yes

Fax:	Yes	***Manual***
	All	No

Medical Director, Dante A. Ragasa, MD.