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# *Candida* Infections of the Genitourinary Tract

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## INTRODUCTION

*Candida* spp. are the most common cause of fungal infections (205), leading to a range of life-threatening invasive to non-life-threatening mucocutaneous diseases. Among *Candida* spp., *Candida albicans* is the most common infectious agent. This dimorphic yeast is a commensal that colonizes skin, the gastrointestinal and the reproductive tracts. Non-*C. albicans* species are emerging pathogens and can also colonize human mucocutaneous surfaces (231). Consequently, they are also isolated in the setting of candidiasis, albeit at a lower frequency. The pathogenesis and prognosis of candidial infections are affected by the host immune status and also differ greatly according to disease presentations. Therefore, diagnosis, management, and treatment choices vary and need to be considered in the overall setting of the affected human host.

Mucocutaneous candidiasis can be divided into nongenital disease and genitourinary disease. Among nongenitourinary candidiasis, oropharyngeal manifestations are the most common and usually are diagnosed in immunocompromised patients, such as human immunodeficiency virus (HIV)-infected persons (extensively reviewed in reference 71). The most frequent manifestations of genitourinary candidiasis include vulvovaginal candidiasis (VVC) in women, balanitis and balanoposthitis in men, and candiduria in both sexes. These diseases are remarkably common but occur in different populations, immunocompetent as well as immunocompromised. While VVC affects mostly healthy women, candiduria is commonly diagnosed in immunocompromised patients or neonates. In the majority of women, a diagnosis of VVC is made at least once during their childbearing years (239). Among the many causes of vaginitis, VVC is the second most common after bacterial vaginosis and is diagnosed in up to 40% of women with vaginal complaints in the primary care setting (13). *Candida* is also the most common infectious agent causing inflammation of the glans penis (80). Both these diseases are usually diagnosed and treated in the outpatient setting. In contrast to genital manifestations of candidiasis, candiduria is usually diagnosed in elderly hospitalized patients, and *Candida* is the most frequently isolated pathogen in nosocomial urinary tract infections (UTIs). A second patient group at risk is neonates, especially those who receive prolonged antibiotic therapy. We here review the epidemiology, microbiology, risk factors, clinical features, pathogenesis, and treatment strategies for the diverse manifestations of genitourinary candidiasis. This review focuses on the most common manifestations of genitourinary candidiasis and concentrates on VVC and candiduria because few studies on candidal balanitis are published.

## DEFINITIONS AND DIAGNOSIS OF GENITOURINARY DISEASES CAUSED BY *CANDIDA* SPECIES

### Definition and Diagnosis of VVC and RVVC

The presence of *Candida* in the vagina, in the absence of immunosuppression or damaged mucosa, is usually not associated with any signs of disease and is thus referred to as colonization. In contrast to asymptomatic colonization, VVC is defined as signs and symptoms of inflammation in the presence of *Candida* spp. and in the absence of other infectious etiology. Over a decade ago, VVC was classified into uncomplicated and complicated cases, a classification that has been internationally accepted and adapted (189, 239, 287). Uncomplicated VVC is characterized by sporadic or infrequent occurrence of mild to moderate disease caused by *C. albicans* in immunocompetent women. Complicated VVC includes cases of severe VVC, VVC caused by non-*C. albicans* species, VVC associated with pregnancy or other concurrent conditions such as uncontrolled diabetes or immunosuppression, and recurrent VVC (RVVC) in immunocompetent women. RVVC is defined as at least four episodes of VVC during 1 year (239). Women who suffer from RVVC are a separate population of otherwise healthy women and are distinct from women who experience sporadic acute VVC. Long-term suppressive antifungal therapy is commonly required to control RVVC, and recurrence rates of up to 40% to 50% occur after discontinuation of suppressive therapy (242). Compared to the case for women with other chronic vaginal symptoms, symptoms of women with RVVC are reported to have the greatest negative impact on work and social life (183).

About 50% of patients have positive microscopy of a wet mount or saline preparation, where yeast cells and hyphal elements can be seen. A 10% potassium hydroxide (KOH) preparation is more sensitive than a saline preparation in identifying yeast cells or hyphae (235). The vaginal pH is often measured to exclude other infections such as bacterial vaginosis or trichomoniasis in which it is high (>4.5), while it is normal (4.0 to 4.5) in VVC. Vaginal culture is the most accurate method for the diagnosis of VVC and is indicated if microscopy is negative but VVC is suspected or in cases of high risk for non-*C. albicans* VVC. Among the various culture methods, there appears to be no difference between Sabouraud agar, Nickerson's medium, or Microstix-candida medium (235). CHROMagar Candida is a selective fungal medium that includes chromogenic substances allowing for quick identification of several different *Candida* spp. based on their color, which also facilitates the detection of mixed infections with more than one species of *Candida* (185, 196). Antigen detection or serologic tests as well PCR-based diagnosis are either not yet reliable or not clinically useful because they are too sensitive (235).

### Definition and Diagnosis of Candidal Balanitis

Candidal balanitis is defined as inflammation of the glans penis, often involving the prepuce (balanoposthitis), in the presence of *Candida* spp. and the absence of other infectious etiology. Candidal balanitis is generally sexually acquired and is often associated with the presences of diabetes (80). Diagnosis is based mostly on clinical appearance alone but should be confirmed by microscopy and/or culture if other differential diagnoses are considered. The quantity of material that can be collected is often small, and thus the sampling method has a strong influence on the sensitivity of microscopy and cultures (72). The use of an "adhesive tape" method has proven to be more sensitive than swabbing (72).

### Definition and Diagnosis of Candiduria

The definition of candiduria is enigmatic. Although most studies rely on culture, both microscopic visualization in urine and culture of urine could be employed. Of concern is that neither the diagnostic criterion (CFU cutoff) nor the collection technique (suprapubic aspiration versus bag collection) for neonatal urinary candidiasis is standardized. Even in adults, CFU criteria to diagnose candiduria range from $10^3$ to $10^5$ CFU/ml urine. In some studies candiduria is even differentially defined for women and men (57). Treatment trials funded by the National Institutes of Health generally use the lower CFU cutoff ($10^3$) as their definition (241). In addition, in most retrospective studies standard urine cultures were screened for candiduria, which means that urine was cultured on MacConkey and blood agar only. Some laboratories culture urines on Uriselect agar, which is a chromogenic agar that allows the preliminary identification of predominantly bacterial uropathogens (195). Although these culture methods are certainly sufficient to identify bacteria, they may be significantly less sensitive to recover *C. albicans* and non-*C. albicans* species. Consistent with this concern, prospective studies in which urine was cultured on Sabouraud dextrose (SD) agar, a standard fungal medium, have reported higher numbers of non-*C. albicans* species (129, 186). It is noteworthy that the fungal burden could be relevant, because a statistically significant correlation between heavy candiduria ($>10^4$ CFU/ml urine) and a high Pittet *Candida* colonization index ($>0.5$) has been established (46). In summary, variable cutoff definitions and unreliable culture techniques may skew analysis of the incidence and outcome of candiduria. These discrepancies have not been adequately addressed in most studies.

## EPIDEMIOLOGY OF GENITOURINARY CANDIDIASIS

### Incidence of VVC

*Candida* spp., mostly *C. albicans*, can be isolated in the vaginal tracts of 20 to 30% of healthy asymptomatic nonpregnant women at any single point in time and in up to 70% if followed longitudinally over a 1-year period (25, 27). If the balance between colonization and the host is temporarily disturbed, *Candida* can cause disease such as VVC, which is associated with clinical signs of inflammation. Such episodes can happen sporadically or often can be attributed to the presence of a known risk factor, e.g., the disturbance of local microbiologic flora by antibiotic use.

VVC is not a reportable disease and is often diagnosed without confirmatory tests and treated with over-the-counter (OTC) medications, and thus the exact incidence is unknown. It is estimated that around 75% of all women experience at least one episode of VVC during their childbearing years, of whom about half have at least one recurrence (239). We are aware of only two population-based studies describing the incidence of VVC, both of which relied on self-reported information from random samples of women living in the United States. One reported that 55% of female Midwestern university students had at least one episode of VVC by age 25 years (102). The other estimated that 56% of women throughout the United States will experience at least one episode of VVC during their lifetime and that 8% of women experience RVVC (96). Both studies found a significantly higher incidence in African-American than in white American women or women of other races. Although VVC affects women globally, we are not aware of any population-based studies from other countries. Furthermore, large studies from ethnically diverse regions to confirm whether incidence rates of VVC vary according to race are lacking.

### Incidence of Candidal Balanitis

Similar to the vaginal tract but at lower frequencies, the glans of the penis can be asymptomatically colonized with *Candida* spp., which are often sexually acquired. Evidence of yeast colonization has been found in 14 to 18% of men without signs of balanitis, with no significant differences between circumcised and uncircumcised men (63, 209). Interestingly, in contrast to the case for the vaginal tract, only half of the isolates were *C. albicans*. In contrast to the case for VVC, we are not aware of any population-based studies. Thus, even estimates of the incidence of candidal balanitis are unavailable. The diagnosis is mostly based on clinical exam and not confirmed by culture. *Candida* spp. are considered to be responsible for 30 to 35% of all cases of infectious balanitis (3, 72, 154) and for up to 54% for diagnoses based solely on clinical examination (154).

### Incidence of Candiduria

Incidence numbers given for candiduria are dependent on the setting and the population studied and have to be carefully compared because of the above-outlined discrepancies with definitions of candiduria. The general consensus is that candiduria is very common in hospitalized patients (9, 133, 205, 216). There is evidence that the incidence is linked to antibiotic usage (277). In general, most estimates of incidence based on culture results are likely underestimated, because standard urine culture is not very sensitive. One large one-day, point prevalence survey done in 228 hospitals from 29 European countries determined that 9.4% of nosocomial UTIs were caused by *Candida* (35). Depending on the population examined, *Candida* is reported in up to 44% of urine samples sent for culture (190). Two retrospective analyses done in Israel and Italy found much lower rates (0.14 to 0.77% and 0 to 1.4%) in urine cultures from both hospitalized patients and outpatients

TABLE 1. *Candida* spp. identified in women with VVC

| Region | No. of subjects | % With: | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | *C. albicans* | *C. glabrata* | *C. tropicalis* | *C. parapsilosis* | *C. krusei* | Other non-*C. albicans* | |
| US, all states | 93,775 | 89 | 8 | 1 | 2 | | | 271 |
| US, Iowa | 429 | 76 | 16 | 1 | 4 | 4 | 2 | 208 |
| Australia | 1,087 | 89 | 7 | 1 | 1 | 1 | 1 | 116 |
| Italy | 410 | 84 | 9 | 1 | 1 | | 5 | 249 |
| Italy | 909 | 77 | 15 | 2 | 1 | 4 | 1 | 59 |
| Austria | 3,184 | 88 | 3 | <1 | 1 | <1 | 7 | 193 |
| China | 1,070 | 90 | 8 | 1 | 1 | | 1 | 86 |
| India | 215 | 47 | 37 | 6 | 10 | 1 | 2 | 8 |
| Turkey | 240 | 44 | 30 | | | 6 | 19[a] | 45 |
| Nigeria | 517 | 20 | 34 | 18 | 5 | | 24[b] | 187 |

[a] *C. keyfir*, 6%.
[b] *C. guilliermondii*, 18%.

(57, 68). The incidence of candiduria also varies with hospital setting, being most common in intensive care units (ICUs) (216) and among those in burn units (34). Other studies report that 11 to 30% of nosocomial urinary tract infections (UTIs) are caused by *Candida* (87, 161, 205). One large study reports that 11% of 1,738 renal transplant patients had at least one episode of candiduria within 54 days of transplant (214). In the National Nosocomial Infection surveillance done between 1992 to 1997 in 112 ICUs across the United States, *C. albicans* was the most commonly reported pathogen (including bacteria) from urine (21%), constituting more than half of the fungal isolates. Also, *C. albicans* was more commonly reported in catheter-associated UTIs than in non-catheter-associated infections (21% versus 13%, $P = 0.009$). Fungal urinary infections occurred more frequently in patients with urinary catheters than in those without urinary catheters (40% versus 22%, $P < 0.001$) (205). In pediatric ICUs the percentage of candiduria was lower (14.3%) (206). In ICUs, preterm neonates with low birth weight are now routinely treated with fluconazole prophylaxis, which has dramatically decreased the incidence in those patients (112, 126, 134, 136).

## MICROBIOLOGY

### Distribution of *Candida* spp. in VVC

The distribution of *Candida* spp. identified in women with VVC varies widely depending on the locations as well as the populations studied (Table 1). Typically, a single species is identified, but two or more species have been found in the same vaginal culture in a minority of women (2 to 5%) with complicated as well as uncomplicated VVC (86, 208). In the United States, Europe, and Australia, *C. albicans* is the most common species identified in women with VVC (76 to 89%), followed by *C. glabrata* (7 to 16%) (59, 116, 208, 249, 271) (Table 1). The overall percentage of non-*C. albicans* species associated with VVC in these countries/continents ranges from 24% to 11%. Some studies have reported an increasing trend in the occurrence of non-*C. albicans* species over time (47, 249), while a recent U.S. study of over 90,000 samples found a consistent yearly distribution from 2003 to 2007 (271). In contrast to the case in the United States, Europe, and Australia, non-*C. albicans* species, in particular *C. glabrata*, appear to be more commonly associated with VVC in some Asian and African countries (Table 1). In Turkey, India, and Nigeria, cases due to *C. glabrata* range between 30 to 37%, while the *Candida* sp. distribution in China resembles closely the one in the United States. With higher resistance levels of most non-*C. albicans* species to the commonly used azole-based treatments and limited possibilities for yeast identification and susceptibility testing in some of these settings, the consequences for women affected by these strains might be incapacitating.

Higher percentages of non-*C. albicans* species have been isolated in women with RVVC than in women with VVC (40 to 32% versus 20 to 11%, respectively) (116, 184, 208, 249). Other populations with higher rates of non-*C. albicans* species include HIV-infected women (94, 249), women after menopause, and especially women with uncontrolled diabetes irrespective of HIV infection (70, 105). Interestingly, higher percentages of non-*C. albicans* species are associated with increasing age in women with VVC (116, 271). In all of these populations, *C. glabrata* is the most common among the non-*C. albicans* species. These data highlight the importance of determining *Candida* spp. and susceptibilities in women at high risk for non-*C. albicans* VVC in order to provide effective therapy.

Genetic relatedness of *Candida* strains in women with RVVC has been studied, and three scenarios have been entertained. They include VVC strain maintenance without genetic variation, strain maintenance with minor genetic variation, and strain replacement (157). In 18/18 patients with recurrent infections, the same strain was responsible for sequential infections, suggesting that the predominant scenario is strain maintenance. However, 56% of the strains exhibited minor stable genetic variations in sequential isolates. A recent study confirmed strain maintenance with microevolution in the majority of women with recurrent episodes of VVC but also reported strain replacement in 4/24 (14%) (54).

### Distribution of *Candida* spp. in Candidal Balanitis

There is a lack of studies about the distribution of *Candida* spp. in candidal balanitis. Considering the fact that this disease is often sexually transmitted, the distribution of *Candida* species is likely to be similar to that in VVC.

TABLE 2. *Candida* spp. identified in patients with candiduria

| Region | Setting | No. of isolates | % | | | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | *C. albicans* | *C. glabrata* | *C. tropicalis* | *C. parapsilosis* | *C. krusei* | |
| US | 10 medical centers | 861 | 52 | 16 | 8 | 4 | | 133 |
| US, New York | Community and hospital | 55[a] | 54 | 36 | 10 | | | 129 |
| US | Hospitals | 316 | 50 | 21 | 10 | 2 | 2 | 241 |
| US, Wisconsin | Renal transplant | 276 | 35 | 53 | | 4 | | 214 |
| Spain | ICUs | 389 | 68 | 8 | 36 | | | 9 |
| Israel | Community and hospitals | 52[b] | 35 | 15 | 19 | 7 | | 57 |
| France | ICUs | 262[c] | 67 | 22 | 3 | 7 | 2 | 34 |
| India | Community and hospital | 145 | 24 | 21 | 31 | 1 | 1 | 192 |

[a] Fluconazole resistance, 4% for *C. albicans* and 25% for *C. glabrata*.
[b] The species was determined for only a subsample (52 of 283).
[c] Fluconazole resistance, 1% for *C. albicans* and 15% for *C. glabrata*.

### Distribution of *Candida* spp. in Candiduria

Analogous to VVC, the causative species of candiduria can vary in studies. Again, in most studies *C. albicans* dominates and accounts for 50% to 70% of all *Candida*-related urinary isolates, followed by *C. glabrata*, and *C. tropicalis*, which is the third most common species (Table 2). There has also been a steady increase in the incidence of non-*C. albicans* strains producing nosocomial infections (68, 118, 288). In neonates, *C. parapsilosis* has become a dominant fungal species that is associated with candidiasis, including candiduria (152, 264). In a large multicenter study from Spain, *C. albicans* was recovered in 68%, followed by *C. glabrata* (8%) and *C. tropicalis* (4%) (9). In our own study, C. *albicans* was recovered in 54% of the cases, followed by *C. glabrata* (36%) and *C. tropicalis* (10%) (129). As outlined above, it is important to take into consideration that standard urine culture is not very sensitive and may lead to underestimation of candiduria, in particular infections caused by non-*C. albicans* species (113, 186).

Molecular typing of serial *Candida* isolates from patients with candiduria demonstrates that patients continue to have infection or reoccurrence with the same strains (129). Similar to the case for VVC, around 5% to 8% of patients with candiduria will have two or more species simultaneously (133). Strains may differ in phenotypic characteristics such as biofilm (BF) formation; however, it was demonstrated in serial isolates that these characteristics remain stable, analogous to serial *Candida* isolates derived from blood (110, 129).

Molecular typing of *Candida* strains derived from the vaginas of pregnant women indicated that the women, who were followed longitudinally through pregnancy, became symptomatic (average time, 14 weeks) with their colonizing *Candida* strains (62). That study found that five of the eight patients with positive vaginal secretions later showed the presence of the same yeast species in their urine. Therefore, it has been suggested that vaginal *Candida* ascending from the genital to the urinary tract could explain the greater incidence of candiduria in women.

### Antifungal Resistance in *Candida* Isolates from Genitourinary Infections

*In vitro* susceptibility testing for fluconazole by the former National Committee for Clinical Laboratory Standards (NCCLS), now the Clinical Laboratory Standards Institute (CLSI), revealed that 21.1% of vaginal isolates were resistant to fluconazole (25). A second large study of 593 vaginal yeast isolates concluded that resistance to fluconazole and flucytosine was observed infrequently (3.7% and 3.0%, respectively), and the more resistant non-*C. albicans* species were more frequently isolated from women with RVVC (208). Among the different species, elevated fluconazole MICs ($\geq$16 $\mu$g/ml) were observed only in *C. glabrata* (15.2% resistant and 51.8% susceptible-dose dependent), and *C. krusei* (41.7% resistant [considered intrinsically fluconazole resistant] and 50% susceptible-dose dependent). Resistance to itraconazole was observed among *C. glabrata* (74.1%), *C. krusei* (58.3%), *S. cerevisiae* (55.6%), and *C. parapsilosis* (3.4%). These results support the use of azoles for empirical therapy of uncomplicated VVC. Recurrent episodes are more often caused by non-*C. albicans* species, for which azole agents are less likely to be effective (208). However, *in vitro* susceptibility testing of *Candida* isolates from women with complicated VVC showed that fluconazole resistance correlated poorly with clinical response, despite a trend to higher mycological failure rates (243). The reasons for clinical improvement of VVC in patients on fluconazole treatment despite isolation of resistant or relatively resistant *Candida* strains remain unclear but could be related to a partial reduction in the vaginal fungal burden. Thus, susceptibility testing is rarely used in the management of VVC. Nevertheless, in patients with refractory VVC or breakthrough episodes, susceptibility testing is imperative to optimize treatment (226).

Resistance patterns of *Candida* isolates derived from urine are similar to those of vaginal isolates. Antifungal susceptibility in candiduric patients depends largely on the infecting strains. Many laboratories perform standard testing only on non-*C. albicans* strains or only if requested. Since *C. glabrata* infections are more common in candiduric patients than in patients with VVC, the overall percentage of resistant isolates can be expected to be higher in candiduric patients. A large fluconazole prophylaxis study done with neonates concluded that fluconazole resistance did not emerge in those patients (163). As outlined in Table 2, published susceptibilities demonstrate that significant numbers of *C. glabrata* strains are resistant to fluconazole. It is noteworthy that antifungal resistance determination is done on yeast cells in suspension. Patients with indwelling Foley catheters, however, are infected with *Candida* embedded in biofilms. CLSI antifungal testing is done on

TABLE 3. Comparison of risk factors associated with VVC and candiduria

| Risk factor | Association with: | |
|---|---|---|
| | VVC | Candiduria |
| Age | Childbearing years | Elderly and neonates |
| Female gender | Yes | Yes |
| Behavioral | | |
| Sexual practices | Yes | No |
| Host | | |
| Antibiotic usage | Yes | Yes |
| Diabetes | Yes | Yes |
| HIV | Only if advanced | Not known |
| Neutropenia | No | Yes |
| Renal transplant | No | Yes |
| Renal obstruction | No | Yes |
| Indwelling Foley catheter | No | Yes |
| Abdominal surgery | No | Yes |

planktonic logarithmically growing yeast cell populations. In modified antifungal susceptibility testing with *Candida* cells that are biofilm associated and attached to a plastic surface, one can demonstrate that these biofilms are usually resistant to azoles, and a high percentage are even resistant to amphotericin B (AmB), whereas the planktonic phenotype of the same strain remains sensitive to azoles. This may explain persistent or relapsing candiduria in patients without the presence or emergence of antifungal resistance (241).

In summary, due to the increased antifungal resistance of non-*C. albicans* species, their emergence remains a concern. The reason for the considerable higher frequency of non-*C. albicans* species in some countries is unclear. Genetic, immune-based, behavioral, and nutritional factors, among others, have to be taken into consideration.

## PATIENT POPULATIONS AT RISK AND PREDISPOSING RISK FACTORS FOR GENITOURINARY CANDIDIASIS

Genitourinary candidiasis is more commonly diagnosed in women than in men. With respect to patient populations affected as well as predisposing risk factors, candiduria and VVC differ (Table 3).

### Risk Factors for VVC

Although many healthy women develop VVC sporadically, several behavioral and host-related risk factors have been associated with VVC and recurrent episodes. These episodes are caused by *Candida* overgrowth from the gastrointestinal and/or the vaginal tract or through sexual transmission (201). Behavioral risk factors that have been significantly associated with a higher incidence of VVC include frequent sexual intercourse and receptive oral sex, as well as the use of high-estrogen (not low-dose) oral contraceptives, condoms, and spermicides (45, 79, 96, 101). Among university students, tight clothing and type of underwear was not associated with VVC (96), while among women with RVVC the use of panty liners or pantyhose was positively associated with symptomatic recurrence (191).

Host-related risk factors that have been significantly associated with VVC and RVVC include antibiotic use, uncontrolled diabetes, conditions with high reproductive hormone levels, and genetic predispositions (105, 235). Antibiotics alter the bacterial microflora of the vaginal and gastrointestinal tracts and thus allow for overgrowth of *Candida* spp. After antibiotic use, the increase in vaginal colonization with *Candida* spp., mostly *C. albicans*, is estimated to range from 10 to 30%, and VVC occurs in 28 to 33% of cases (235). It is commonly hypothesized that the reduction of lactobacilli in the vaginal tract predisposes women to VVC. Lactobacilli play a key role in the vaginal flora through the production of hydrogen peroxide, bacteriocins, and lactic acid, which protect against invasion or overgrowth of pathogenic species (82, 212). However, studies have failed to provide evidence that an altered or abnormal vaginal bacterial flora predisposes women to recurrent episodes of VVC in the absence of antibiotic intake (237, 272, 295). In fact, a recent prospective study demonstrated that vaginal *Lactobacillus* colonization was associated with a nearly 4-fold increase in the likelihood of symptomatic VVC (168). Episodes of VVC occur mostly during childbearing years and are rare in premenarchal and postmenopausal women. An increased frequency of VVC has been reported during the premenstrual week (79) and during pregnancy (60). Some studies suggest that there might be a genetic predisposition in women who experience sporadic or frequent episodes of VVC. An increased incidence of VVC was found in African-American compared to white American women in two different population-based studies (97, 102). Furthermore, increased incidence of blood group ABO-Lewis nonsecretor phenotype was found in women with RVVC compared to controls (48), and more recently, polymorphism in the mannose-binding lectin gene was found to be associated with RVVC (18, 104). $HIV^+$ women have higher rates of vaginal colonization with *Candida*, often non-*C. albicans* species, than $HIV^-$ women (76, 94, 223, 249). However, in a multicenter cohort study no difference in frequency of VVC between $HIV^+$ women not receiving antiretroviral therapy and $HIV^-$ women was found (223). Similar to other genital diseases that cause damage of the mucosa, VVC has been associated with increased vaginal HIV shedding (274) and in a recent meta-analysis was found to be associated with a 2-fold increase in the risk of HIV acquisition (213).

### Risk Factors for Candidal Balanitis

Predisposing risk factors include diabetes mellitus, immunosuppression, and being uncircumcised (80, 154). Furthermore, being uncircumcised is considered to be a major predisposing factor for candidal balanoposthitis when associated with poor hygiene and buildup of smegma.

### Risk Factors for Candiduria

Most risk factors associated with candiduria differ considerably from the ones associated with VVC, although a few, such as prior antibiotic use and uncontrolled diabetes, are similar (Table 3). The majority of clinical studies have identified similar risk factors associated with candiduria in adults. They include anatomic urinary tract abnormalities, comorbidities, indwelling urinary drainage devices, abdominal surgery, ICU

admission, broad-spectrum antibiotics, diabetes mellitus, increased age, and female sex (9, 87, 108, 133, 161). Even in the subgroup of renal transplant patients, who compromise only a small fraction (0.9 to 3%) of patients with candiduria, these risk factors prevail (214). Only one large study has compared risk factors in community-acquired versus nosocomial candiduria. They report that patients who present from the community with candiduria are younger, more commonly female, pregnant, and, interestingly, more likely to have dysuria. A second patient population at risk are prematurely born neonates, especially those who received antibiotic treatment and have indwelling lines (111, 135, 159, 164, 165). In pediatric patients the mean rate of urinary catheter utilization in pediatric ICUs is lower than that in medical ICUs, which may in part explain the lower number of candiduria cases in these patients (206).

Most studies do not differentiate among the different species that can cause candiduria, in part because the species of the non-*C. albicans* species are often not determined. In two case-control studies designed to compare risk factors for catheter related nosocomial candiduria caused by *C. albicans* versus *C. glabrata* at a tertiary hospital in Boston, it was found that risk factors were similar except that fluconazole and quinolone use was associated more with *C. glabrata*-mediated candiduria (109). In other studies, one in renal transplant patients and one in ICU patients, this association of quinolone and fluconazole usage has not been documented as a risk factor for *C. glabrata*-mediated disease (9, 214).

## CLINICAL PRESENTATION OF GENITOURINARY CANDIDIASIS

Despite the vicinity of the two niches (bladder and vagina) the clinical presentations of the diseases differ greatly.

### Clinical Presentation of VVC

The clinical symptoms of VVC are nonspecific and can be associated with a variety of other vaginal diseases and infections, such as bacterial vaginosis, trichomoniasis, *Chlamydia* infection, and gonorrhea. Vulvar pruritus and burning are the hallmark symptoms in most women with VVC, frequently accompanied by soreness and irritation leading to dyspareunia and dysuria (13). On physical exam, vulvar and vaginal erythema, edema, fissures, and a thick curdy vaginal discharge are commonly found (79).

### Clinical Presentation of Candidal Balanitis

As with VVC, the clinical signs and symptoms of candidal balanitis are often nonspecific and could be due to a variety of other causes, such as infections with bacteria or noninfectious causes (80). Patients commonly complain of local burning and pruritus, and the clinical features include mild glazed erythema and papules with or without satellite-eroded pustules (154).

### Clinical Presentation of Candiduria

Fungal urinary tract infections are mostly asymptomatic (205). This means the majority of patients have neither fever, dysuria, nor any other urinary tract-related complaint. Leukocyturia, which is also not part of the definition criteria of asymptomatic bacteriuria, is mostly not present in candiduric patients. *C. albicans* UTIs are commonly catheter associated (205, 206). Candiduria occurs late in the hospital stay. In a large prospective study done in French ICUs, the mean interval between ICU admission and candiduria was 17.2 ± 1.1 days, and similar numbers were reported in studies from Spain (9, 34). In renal transplant patients, the first episode occurred a median of 54 days after transplantation (range, 0 to 2,922 days) (214). In these patients candiduria is also mostly asymptomatic. Candiduria can be the result of uncomplicated cystitis and/or pyelonephritis, analogous to bacteriuria. In contrast to bacteriuria, the majority of candiduric patients do not present with concomitant septicemia. Studies report that a low percentage (1 to 8%) of candiduric patients develop candidemia and that ICU patients with candiduria carry the highest risk to become candidemic (34, 35, 133, 214).

The differentiation between upper and lower urinary tract infections has been inherently difficult to make. A small imaging study using white blood cells labeled with indium-111 concluded that 50% of the studied patients ($n = 8$) with candiduria showed renal uptake in $^{111}$In-labeled leukocyte scintigraphy, with uptake persisting after antifungal treatment (107). This study excluded patients with concomitant bacteriuria, patients on antifungal treatment, and patients in the ICU setting. This finding should be confirmed in a larger study, as it raises the concern that subclinical pyelonephritis may be more frequent in patients with candiduria than thought. The diagnostic value of single amphotericin washout in candiduria to predict kidney infection or invasive candidiasis is low, as the positive predictive value is only 44% (95). Data from experiments in rabbits suggests that detection of renal *Candida* casts may be a useful diagnostic marker in distinguishing upper versus lower urinary tract candidiasis (178), but the frequency of this finding is unknown (16, 106). One study suggests that the D-arabinitol/creatinine ratio could be used to differentiate between *Candida* pyelonephritis and colonization (261). However, in that study the clinical distinction between pyelonephritis and colonization was poorly documented.

Prostatitis and epididymitis can also lead to candiduria (282). They are more common in older or immunocompromised men and should be evident by careful clinical examination. In some cases these patients develop an abscess in the tissue.

Candiduria rarely is associated with pneumaturia, which is the result of emphysematous tissue invasion or perinephric abscess formation (254). These complicated urinary tract infections are observed predominantly in diabetic patients (74, 114, 211, 252) and can also occur in the setting of prostatitis and epididymitis. In summary, most patients with candiduria have few or no symptoms, which complicates treatment decisions, as outlined below.

## MORBIDITY, MORTALITY, AND ASSOCIATED COSTS

Although not associated with any mortality, VVC and RVVC are associated with considerable morbidity. Symptoms of vaginitis can cause substantial distress, resulting in time lost from work and altered self-esteem (77). Thus, it is not surpris-

ing that vaginal complaints are the most common reason for gynecological consultation. Among the many causes of vaginitis, VVC is the second most common after bacterial vaginosis, and it is diagnosed in up to 40% of women with vaginal complaints in the primary care setting (13). In the United States, prior to the availability of OTC treatment, approximately 13 million cases of VVC annually accounted for 10 million visits to the gynecologist (138). In 1990, the first topical treatment for VCC was approved by the Food and Drug Administration for OTC use, and since then the combined antifungal prescription and OTC sales have almost doubled (153). In 1995 alone, the annual cost of VVC was estimated to be $1.8 billion, with approximately half of this amount consisting of charges for doctor visits (97). Furthermore, industry sources report that in 1995 OTC sales of vaginal antifungals were the largest component of the feminine health care sales in drugstores, generating nearly 60% of the category's sales and resulting in approximately $290 million (75a).

Despite the lack of symptoms, most studies that compare mortality of candiduric patients with that of an appropriate control patient cohort demonstrate increased mortality in candiduric patients relative to the control population (9, 133, 241). Given that these patients are usually very sick, it remains difficult to determine to what extend candiduria contributes to the death of these patients. Despite controlled retrospective studies, confounding factors cannot be ruled out. An increased colonization burden may predispose them to invasive candidiasis. Eight percent of candiduric patients developed candidemia with the same species in one prospective multicenter study (which included 24 ICUs) from France (34). In a large Spanish study, in-hospital mortality was 48.8% in patients with candiduria compared to 36.6% in those without candiduria ($P < 0.001$) (9). Significant differences were also found for ICU mortality (38% versus 28.1%, $P < 0.001$) in that study. A study done in French ICUs also concluded that the crude mortality was 31.3% for candiduric patients (34). In a similar manner, increased mortality is found in candiduric renal transplant patients (2, 214). In contrast, Sobel et al. did not observe complications of fungal urinary tract infection in over 330 hospitalized patients (not only ICU patients), including pyelonephritis, candidemia, systemic candidiasis, and fungus-related death (241). They concluded that asymptomatic or minimally symptomatic candiduria in itself was usually benign. In a large review of candidemic subjects, Ang et al. concluded that candidemia was rarely the consequence of candiduria and usually occurred only in the presence of upper urinary tract obstruction (14).

Candiduria is one of the most common nosocomial infections. The cost that it inflicts upon the health care system is not known. Conservative estimates calculate a rise of the mean hospital cost by $1,955 for nosocomial UTIs (52). In cases where candiduria leads to candidemia, the costs would rise dramatically, since candidemia results in an increase of per-patient hospital charges of up to $39,331 for adults and $92,266 for children (204, 289). Given new developments where hospitals are not to be reimbursed for nosocomial infections, it will become essential to define asymptomatic and symptomatic candiduria better so that unnecessary treatment, catheter changes, and hospital prolongation can be avoided, especially since these costs will have to be absorbed by hospitals.

## PATHOGENESIS OF GENITOURINARY CANDIDIASIS

### Animal and Other Models for Genitourinary Candidiasis

**Rodent models for VVC.** Murine and rat models have been valuable in advancing our understanding of *Candida* pathogenicity, antifungal pharmacokinetics, and the immune responses to *Candida*, including *Candida* vaginitis (reviewed in references 43, 88, and 177). Infection with *C. albicans* in these rodents is a *de novo* event in a naïve host which differs significantly from humans, who develop immune responses to *Candida* early in life, as *C. albicans* is a commensal organism of the gastrointestinal tract and often of the genital tract (43, 88, 198).

Experimental *Candida* vaginitis in rodents typically requires a large intravaginal inoculum of $10^5$ to $10^6$ organisms, while the number of *Candida* cells that cause disease in humans is not known (43, 88, 198). In humans, VVC often results in the inability to control fungal growth of the resident *Candida* strains from the vaginal and/or intestinal reservoir and thus triggers the disruption of the fine balance between commensalisms without tissue damage and disease. Furthermore, experimental infection in rodents is either self-healing or persistent with a low fungus burden, and in both cases it effectively immunizes the animals against any secondary challenge (42, 92, 93). Thus, there are no rodent models that allow for the study of RVVC, the clinically most relevant and difficult-to-manage condition. In addition, experimental *Candida* vaginitis in rodents requires estrogen induction to mimic human conditions. This estrogen administration results in a vaginal epithelium that is thicker and fully keratinized and thus allows for fungal attachment, growth, and biofilm formation (49, 140). The keratin layer enhances hypha formation, adherence, and Sap production, and the estrogens down-modulate cell-mediated immunity and reduce leukocyte infiltration, which helps the development of disease (124, 140). The facts that rodents' susceptibility to *Candida* infection strongly correlates with estrogen sensitivity (56) and that VVC in humans is commonly associated with phases in life that are influenced by estrogens, such as childbearing years and pregnancy (77, 235), support some validity of using rodent models.

**Primate models for VVC.** In contrast to rodents, healthy nonhuman primates have shown to be colonized with *Candida* spp. and to develop mucocutaneous candidiasis and thus might be better models than rodents (253). Intravaginal inoculation at dosages of $5 \times 10^6$ *C. albicans* blastoconidia with and without intravenous concurrent estrogen administration resulted in successful vaginal infection of one type of macaque species (rhesus) but not another, a finding which was unexpected, with the different susceptibility remaining unexplained. However, despite successful *C. albicans* infection with demonstrable vaginal cytokine responses, the rhesus macaques did not show any signs or symptoms of vaginitis, the hallmark of human disease. Therefore, despite fewer limitations than with rodent models, primate models still have important limitations regarding the understanding of the pathogenesis and immunity associated with human VVC.

**Vaginal tissue models for VVC.** Efforts have also been made to reproduce the vaginal infection in *in vitro* studies by using reconstituted human vaginal epithelial tissue (217–219) or vaginal tissue sections (66). Valuable information has been ob-

tained, but the limitations of in *vitro* results under well-controlled conditions, in the absence of estrogenic conditioning and immune control, have to be kept in mind when making comparisons to *in vivo* conditions.

**Rodent models for candiduria.** Candiduria has been infrequently studied in animal models. Bacterial UTI has been studied in rodents, dogs, and pigs, but candiduria has been studied predominantly in rats, mice, and rabbits. In these animal experiments, renal candidiasis is achieved mostly by intravenous infection of the yeast (181). This route of infection may not mimic the pathogenesis adequately, because natural infection, especially in the setting of an indwelling catheter, is most often the result of an ascending infection.

In mice, large doses of *C. albicans* injected intravenously cause generalized candidiasis and multiple organ involvement, whereas smaller doses produce transient candidemia and only isolated renal involvement (50, 123). These studies suggest also that renal involvement starts as an acute pyelonephritis leading to multiple cortical abscesses and scarring within 9 to 11 days after inoculation. At that stage candidal mycelia can be identified within the tubular lumen of the renal medulla, and local proliferation leads to papillary necrosis, bezoar formation, and obstructive uropathy (50, 123). Alternatively, it has been suggested that isolated renal involvement may represent an ascending infection. Murine models have also been used to examine the effects of treatment with antifungals and temperature on the course of infection (139, 263). In rats, the effect of ureteral obstruction on the course of renal candidiasis has been demonstrated, using both normal and diabetic Sprague-Dawley rats. Mean CFU were similar in obstructed and control rats but higher in diabetic rats regardless of the presence of ureteral obstruction. An effect of amphotericin B treatment could also be demonstrated, and in general rat models have been helpful to determine adequate drug levels (65, 259).

**Rabbit models for candiduria.** Rabbit models are an alternative to rodent models, as they allow more easily the analysis of candiduria and catheter placement (178, 179). In studies on candiduria, rabbits were usually injected intravenously with *Candida*, in contrast to ascending UTI models with bacteria which were described almost 100 years ago. Thus, rabbits have often been used to draw conclusions on candiduria as a result of hematogenous spread, which represents the minority of cases. With this model, e.g., it was established that urinary concentrations of *C. albicans* were not predictive of the fungal burden in the kidney and that negative urine cultures in rabbits did not rule out renal candidiasis. Also, rabbits have been used to examine the relevance of casts and quantitative urine cultures (178, 179). Finally, rabbit models can be more convenient for pharmacodynamic studies.

**Primary human cells, cell lines, and reconstituted epithelium as models for candiduria.** Human renal epithelial and uroendothelial cells can be isolated from normal human tissue, cryopreserved immediately, and delivered frozen. Human renal epithelial cells are capable of internalizing bacteria (188). They can produce cytokines and chemokines and actively participate in acute inflammatory processes by affecting, e.g., leukocyte chemotaxis via the production of interleukin-8 (IL-8) (222). Human urothelial cells also release inflammatory mediators. In addition, the urothelial cell line TEU-1 was established from a healthy human ureter, and followed by immortalization, it can be used to address specific questions (141). In the last few years more sophisticated *in vitro* systems have been developed and neobladders have been reconstructed *in vitro* by culturing urothelial cells on collagen matrix to reproduce normal bladder mucosa. This culture technique leads to the formation of wide pluristratified epithelial sheets, resembling the normal transitional epithelium (64). In summary, these *in vitro* cells provide a useful *in vitro* model to study the relationship between renal epithelial cells, uroendothelial cells, and reconstituted transitional epithelium with pathogens.

In summary, results from rodent models allow for understanding of some aspects of pathogenesis of human disease. However, due to the lack of prior colonization, these animals usually have to be immunosuppressed to achieve persistent infection (273). As *Candida* is not a commensal, the host response will be different and involve more immune sensitization. Therefore, rodent models must be viewed in light of these important limitations. Rabbits are valuable, especially for pharmacokinetic studies, because longer courses of antifungal therapy can be administered. However, due to high costs, only limited numbers of animals can be studied. *In vitro* models can be used for effective high-throughput screening for novel antifungal agents and to study the inflammatory response.

TABLE 4. Virulence traits of *Candida* spp.

| Virulence trait | Presence in: | |
|---|---|---|
| | *C. albicans* | *C. glabrata* |
| Bud-hypha transition | Present | Present |
| Proteases | Sap, Plb | Yps |
| Adhesion proteins | Als | Epa |
| Biofilm formation | Present | Present |
| Phenotypic switching | White to opaque | Core switching |

## *CANDIDA* VIRULENCE TRAITS RELEVANT FOR GENITOURINARY DISEASE

Using the above-discussed infection models in addition to molecular tools and microarrays, distinct stages of infections of both superficial and invasive *Candida* disease have been investigated (220, 221). There is a paucity of studies done on candiduria. However, virulence attributes have been investigated in other mucosal candidiasis models, including VVC. Importantly, recent studies suggest that the presence of vaginal *Candida* strains with enhanced virulence and tropism for the vagina correlates with the severity of VVC in humans (149). From these studies we have learned of *Candida's* exceptional adaptability by rapid alterations in gene expression in response to various environmental stimuli. Many attributes contribute to *C. albicans* virulence, among them adhesion, hyphal formation, phenotypic switching (PS), extracellular hydrolytic enzyme production, and biofilm formation (Table 4).

### Bud-Hypha Formation in *Candida* spp.

*C. albicans* is both a commensal and a pathogen that can exhibit yeast, hyphal, or pseudohyphal morphology. These morphological transitions promote colonization and invasion at different anatomical sites. They also occur in other *Candida*

spp. The yeast form is associated with dissemination and the hyphal form with adhesion, tissue invasion, and proteolytic activity (281). Accordingly, genes involved in these functions (*ALS3*, *SAP4* to *-6*, *HWP1*, *HYR1*, and *ECE1*) are differentially expressed (20, 28, 120, 215, 251). The mitogen-activated protein (MAP) kinase, cyclic AMP (cAMP), and pH-sensing Rim101 signal transduction pathways regulate cellular morphology and expression of hypha-associated genes (281). Some alternative therapy regimens have been investigated because they claim to inhibit the bud-hypha transition (4). The bud-hypha transition may also contribute to virulence of other *Candida* species such as *C. glabrata* (144). Even though *C. glabrata* strains do not exhibit germ tube formation in classical mycological assays (210), the majority of clinical strains undergo coreswitching and in that process exhibit pseudohypha formation and tube formation, demonstrating that these developmental programs are general characteristics of most strains of *C. glabrata* (144).

### Aspartic Proteinases and Phospholipases in *Candida* spp.

The extracellular hydrolytic enzymes, including the secreted aspartyl proteinase (*SAP*) and phospholipase (*PLB*) gene products, have been shown to directly contribute to *C. albicans* virulence (31, 32, 40, 61, 173). *C. albicans* possesses at least 10 members of a *SAP* gene family, all of which have been sequenced and extensively characterized. Saps contribute to the virulence of *C. albicans* in animal models of infection. Four types of phospholipases have been reported in *C. albicans*, i.e., phospholipases A (15), B (22, 117) C (200), and D (122), but only the *PLB1* and *PLB2* gene products have been detected extracellularly. Although *PLB1* is thought to account for most of the secreted phospholipase B activity in *C. albicans*, *PLB2* contributes in a minor way, because a *PLB1*-deficient strain still produces residual amounts of phospholipase B activity (103). The *in vivo* expression of the *C. albicans SAP1* to *SAP8* and *PLB1* and *-2* genes was analyzed in 137 human subjects with oral or vaginal candidiasis or *Candida* carriage by reverse transcription-PCR (RT-PCR) using specific primer sets. A spectrum of *SAP* gene expression profiles was obtained from different *C. albicans* strains during symptomatic disease and asymptomatic carriage. During both disease and carriage *SAP2* and *SAP5* were the most commonly expressed genes. Also, it was found that *SAP1*, *SAP3*, *SAP4*, *SAP7*, *SAP8*, and *PLB1* expression was correlated with oral disease. Furthermore, *SAP1*, *SAP3*, and *SAP8* were preferentially expressed in vaginal rather than oral disease. Other human studies also reported differential expression of Saps in patients with VVC and RVVC or asymptomatic carriers (150, 151, 176). Antibodies (Abs) that bind to Sap2 have shown to be protective in certain models for VVC (66). In *C. glabrata* the glycosylphosphatidylinositol-linked aspartyl proteases (Yps) is linked to virulence (137).

### Adhesion Proteins in *Candida* spp.

Many genes are implicated in participation in adhesion to epithelial cells (39, 99, 175, 268). The *C. albicans* agglutinin-like sequence (*ALS*) family includes eight genes that encode large cell surface glycoproteins. Although adhesive function has been demonstrated for several Als proteins, the dissection of their role in *C. albicans* pathogenesis is very complex because of extensive allelic variation, strain differences (162), different models, and complex interplay (119). The role of Als1p has been evaluated most thoroughly. Mice injected with a *C. albicans* Als1/Als1 strain lived longer, and the disease developed slower in the initial 28 h after intravenous (i.v.) injection, than mice injected with the wild-type control strain (98, 160). Decreased virulence was also demonstrated in the early stages in a model of oral candidiasis (130). Also, loss of Als3p was noted to affect adhesion more than loss of Als1p (291). Other Als proteins have in part given conflicting results (291–294). Importantly, an anti-*C. albicans* vaccine composed of the recombinant N terminus of Als1p (rAls1p-N) reduces CFU and improves survival in both immunocompetent and immunocompromised mice (248). Newer trials report that vaccination of mice with rAls3p-N induces a broader Ab response than rAls1p-N and a similar cell-mediated immune response (247). This vaccine was especially more effective than rAls1p-N against oropharyngeal or vaginal candidiasis.

In *C. glabrata*, *EPA1* encodes a glycosylphosphatidylinositol (GPI)-anchored cell wall protein (Epa1), which is important for adhesion to uroepithelial cells in a murine model (73). In *C. glabrata* strains, 21 paralogues of *EPA1* are characterized, all encoding proteins highly related to Epa1. Most of these *EPA* genes are located in subtelomeric position where they are transcriptionally silenced (44). Transcription of some subtelomeric *EPA* genes can be derepressed by limitation of $NAD^+$ precursors (73). Genetically engineered strains that have either *SIR3*, *SIR4*, or *RIF1* deletions overexpress many *EPA* genes, resulting in a hyperadherent phenotype of the *C. glabrata* strain (44, 69, 125).

### Biofilm Formation in *Candida* spp.

Surface-associated *Candida* can grow embedded in extracellular matrix that is composed of carbohydrates and proteins and is referred to as a biofilm. Biofilms (BFs) form readily on plastic surfaces such as Foley catheters and intrauterine devices (IUDs), and they render the embedded *Candida* isolates resistant to antifungal reagents, especially azoles. BF can also form on the mucosal surfaces and promote persistence of fungal infection (228). Formation of BF among individual *Candida* strains can differ greatly, and urinary isolates can be differentiated into low and high BF formers. Furthermore, BF appears to be a strain-specific characteristic that does not change during chronic infection (129). Other *Candida* spp. (110) can also form BF with extracellular matrix, although BF-associated gene regulation is studied predominantly in *C. albicans*, which is reviewed extensively elsewhere (29). Two transcription factors, Tec1 and Bcr1 (182, 225), regulate hypha-specific genes and genes downstream of hyphal differentiation. *Candida* genes that control adherence, attachment hyphal formation, and quorum-sensing molecules also regulate BF.

### Phenotypic Switching in Diverse *Candida* spp.

Phenotypic switching (PS) alters virulence and was first described in *Candida* strains 20 years ago (229, 230). In *C. albi-*

*cans* isolates derived from VVC, phenotypic switching could be demonstrated and also occurred during treatment relapses (245). The WO-1 strain is a model strain for reversible white-to-opaque switching (WOS). White-phase cells are round, and opaque-phase cells are elongated (12). Opaque-phase cells are mating competent, whereas white-phase cells survive better within the mammalian host but can switch to mating-competent cells when needed (172). Clinical isolates can undergo WOS if they are homozygous (**a**/**a** or α/α), whereas heterozygous (**a**/α) strains cannot switch (147, 156). The precise contribution to pathogenesis of VVC and recurrent VVC is still not clear (244, 246). Wor1 has been identified as a master regulator of WOS, as its deletion blocks WOS (121). The genes *MTL***a***1*, *MTL*α *2*, *WOR1*, *CZF1*, *WOR2*, and *EFG1* constitute a circuit that regulates WOS (296, 297). White-phase cells are more virulent in i.v. infection (143), and opaque-phase cells colonize skin better (144). WOS also affects other virulence traits, including the bud-hypha transition (10), sensitivity to neutrophils and oxidants (142), antigenicity (11), adhesion, secretion of proteinase (174, 270), drug susceptibility, and phagocytosis by macrophages (158). All of these altered traits can potentially affect survival in specific niches of the mammalian host and promote chronic infection.

The relevance of phenotypic switching for pathogenesis in other *Candida* species is less well understood. The majority of clinical *C. glabrata* strains undergo "core switching" on agar containing $CuSO_4$ (144–146). Core switching results in white (W), light brown (LB), dark brown (DB), very dark brown (vDB), and irregular wrinkle (IWr) colonies. DB predominates among natural isolates and in mice has a colonization advantage over other colony types (250). Phenotypic switching occurred in *C. glabrata* strains of patients with VVC, and although the DB colonies predominated, different switch phenotypes could simultaneously dominate different body locations in the same host (38). Mating type switching demonstrated at both the genetic and transcription levels occurred in one host. In *C. lusitaniae*, a rare pathogen in candiduria that can undergo phenotypic switching, a high amphotericin resistance is associated with W, whereas low amphotericin resistance and filamentation are associated with LB and DB colonies (171). Hence, it is proposed that phenotypic switching may confer a selective advantage in a host that is treated with amphotericin.

## HOST IMMUNE RESPONSES IN GENITOURINARY CANDIDIASIS

All manifestations of candidiasis (whether superficial or invasive infections) are dependent on the host, and therefore the host's immune response is a crucial element of pathogenesis and host-pathogen interaction (207). The state of commensalisms is temporarily disturbed when *Candida* causes disease such as VVC, while in RVVC this balance may be more permanently disturbed. With respect to genitourinary candidiasis, there is an impressive body of literature on host immune responses to VVC (most recently reviewed in references 43 and 88). In contrast, there are virtually no studies done on the host response to candiduria, and therefore the distinction between disease and commensalism in this disease has remained enigmatic.

### Cell-Mediated Immune Responses to VVC

Despite the early hypotheses that cell-mediated immunity plays a major role in all forms of mucosal candidiasis, the general consensus today is that women with RVVC do not have a defect in their systemic cell-mediated immunity and that the immune deficiencies reside locally (88). T cells can be demonstrated in large numbers in the human vagina, and their characteristics suggest that they migrate to the vaginal epithelium in response to local antigenic stimuli and/or inflammatory chemokines (43, 199). However, their exact role in VVC and RVVC is not clear.

### Humoral Immune Responses to VVC

Similar to T cells, B cells and immunoglobulin (Ig)-secreting plasma cells, which are normally absent in the healthy vagina, are recruited into the vaginal tissue following antigenic stimulation (124, 199). Anti-*Candida* IgG and IgA have been identified in the sera and cervicovaginal secretions of women with and without RVVC (30, 67, 166, 170). While serum anti-*Candida* IgA and IgG levels appear to be similar in women regardless of a history of RVVC, some studies have shown higher levels of vaginal anti-*Candida* IgA and IgG in women with RVVC than in those without RVVC (67), whereas others have not found such differences (30, 91, 170). Thus, a potential role of local Abs in RVVC is dismissed by most authors. However, neither the specific types of *Candida* antigens that these vaginal Abs respond to nor their affinity or function has been studied, and thus their potential role in the pathogenesis of RVVC remains unclear (43). This is important to keep in mind, as a number of various Abs have shown to be protective against *Candida*-associated disease, systemic as well as mucosal (43), and human domain Abs against virulence traits of *C. albicans* have recently been shown to inhibit fungal adherence to vaginal epithelium and protect against experimental vaginitis in rats (66).

### Hypersensitivity Reactions to VVC

Several studies suggest that about a quarter, or even more, of women with RVVC could have an allergic component contributing to the etiology and/or severity of their disease (85, 202, 278, 283, 284). These studies have shown higher levels of eosinophils, *Candida*-specific IgE, and/or prostaglandin $E_2$ in the vaginal secretions of women with RVVC compared to women without RVVC. This is further supported by the clinical response of 30% of women with RVVC to an antiallergic treatment with the leukotriene receptor antagonist zafirlukast (280). However, all of these studies had some methodological limitations.

### Innate Immune Responses to VVC

Studies by Fidel and coworkers suggest that vaginal epithelial cells play a crucial role in the defense mechanisms against VVC (21, 88, 89). Based on data from a human life challenge model, these authors hypothesize that following the interaction of *Candida* with vaginal epithelial cells, VVC is associated with signals that promote a nonprotective inflammatory leukocyte response and concomitant clinical symptoms (21, 88, 90). They

TABLE 5. Intravaginal agents for treatment of uncomplicated VVC

| Drug | Formulation | Dose | Duration (days) | Prescription status |
|---|---|---|---|---|
| Butoconazole | 2% cream | 5 g daily | 3 | OTC |
| | 2% sustained release cream | 5 g | 1 | Prescription |
| Clotrimazole | 1% cream | 5 g daily | 7 | OTC |
| | 2% cream | 5 g daily | 3 | OTC |
| | 100-mg vaginal tablet | 1 tablet | 7 | OTC |
| | 100-mg vaginal tablet | 2 tablets | 3 | OTC |
| Miconazole | 2% cream | 5 g daily | 7 | OTC |
| | 100-mg vaginal suppository | 1 suppository | 7 | OTC |
| | 200-mg vaginal suppository | 1 suppository | 3 | OTC |
| | 1,200-mg vaginal suppository | 1 suppository | 1 | OTC |
| Nystatin | 100,000-unit vaginal tablet | 1 tablet | 14 | Prescription |
| Tioconazole | 6.5% ointment | 5 g | 1 | OTC |
| Terconazole | 0.8% cream | 5 g | 7 | Prescription |
| | 0.8% cream | 5 g | 3 | Prescription |
| | 80-mg vaginal suppository | 1 suppository | 3 | Prescription |

suggest that resistance to VVC is associated with a lack of such signals and/or antifungal activity of vaginal epithelial cells. Furthermore, these studies indicate that neutrophils contribute to the pathogenesis and local inflammation in VVC. Such conclusions are supported by the fact that neutropenia, a major risk factor for disseminated candidiasis, is not a risk factor for VVC (Table 3).

Mannose-binding lectin (MBL) is an epithelial cell-associated host protein, binds to *Candida* mannan, activates complement, and thus inhibits *Candida* growth. Reduced levels of MBL and genetic polymorphism in the MBL gene were found in Chinese and Latvian women with RVVC (18, 104, 155).

### Immune Responses to Candiduria

Although candiduria and VVC affect neighboring mucosal surfaces, the anatomy of the mucosal surfaces and their local microenvironments are very different. For example, the vaginal microenvironment is an estrogen-controlled environment, while the bladder milieu has a high urea content. To what extent the host's presiding defense mechanisms differ greatly needs to be further investigated. As opposed to the vagina, the urinary tract is sterile. Most candiduria manifests as cystitis or pyelonephritis as a result of an ascending infection. In an ascending UTI, the first line of defense that the pathogen encounters is the one provided through the mucosa of the urinary tract. However, the response of the urinary tract mucosa to *Candida* has not been studied. Abs can inhibit microbial adherence to mucosal surfaces (255, 256). Immunization eliciting such Abs has been shown to protect against bacterial UTIs in monkeys (267). In adults, a vaginally administered vaccine has proven to be protective against reinfections in phase II trials (266). All of these studies are done in bacterial UTI models, but Epa proteins of *C. glabrata* have also been demonstrated to mediate adherence and could potentially be blocked by Abs (73). Another focus in research of bacterial UTIs has been the identification and quantification of Ab-secreting cells, including their lymphocyte homing receptors, in the blood of patients with pyelonephritis as an indicator of local immune response (131, 132). In candiduria the serological response has been investigated, but clear correlations with invasive disease were not established (262). Another element of the host response in UTI are defensins (290). The protective role of β-defensins against oral microbes, including *Candida*, has been studied only in oral epithelia (5). The role of other important proteins that have immune-modulatory capacity in bacterial UTIs, such as the Tamm-Horsfall, is not known for candiduria (5, 115, 290). As *Candida* is a commensal in the vaginal but not in the urinary tract, mechanisms of local mucosal immunity may not be the same.

## TREATMENT OF GENITOURINARY CANDIDIASIS

### Treatment of VVC

Treatment recommendations for VVC are separated into treatment of uncomplicated VVC caused by *C. albicans* and of complicated VVC, which includes RVVC, severe VVC, VVC caused by non-*C. albicans* species, and VVC in immunocompromised hosts (189, 287). In cases of complicated VVC, contributing factors such as diabetes or behavioral factors should be controlled or avoided. Treatment should not differ on the basis of HIV infection (189).

**Treatment of uncomplicated VVC.** Successful treatment of uncomplicated VVC is achieved with single-dose or short-course therapy in over 90% of cases. Several topical and oral drugs are available, without evidence for superiority of any agent or route of administration (189), although among the topically applied drugs, azoles are more effective than nystatin (287). Table 5 summarizes the intravaginal treatment options recommended by the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA). As an oral agent, fluconazole at 150 mg as a one-time dose is recommended for uncomplicated VVC (189, 287). Be-

cause oral and topical antimycotics have shown to achieve equivalent results for the treatment of VVC (276), both fluconazole given orally and topical agents have received the same recommendation in the IDSA guidelines (A-1), and no preference is given to either treatment (189).

**Treatment of complicated VVC and RVVC.** Complicated VVC with azole-susceptible strains requires topical therapy administered intravaginally daily for at least 7 days or multiple doses of oral fluconazole (150 mg every 72 h for three doses) (234, 240). In cases of RVVC, this regimen followed by long-term weekly treatment with fluconazole at 150 mg orally has shown to significantly reduce recurrence rates compared to three doses of fluconazole alone (242). Long-term suppressive therapy with oral fluconazole is the most convenient and well-tolerated regimen among other options and was shown to be effective in over 90% of patients with RVVC. Against expectations, patients on suppressive therapy with fluconazole have shown little evidence of developing fluconazole resistance in *C. albicans* isolates or superinfection with non-*C. albicans* species (226, 242). However, species identification and MIC testing should be performed in women experiencing breakthrough or refractory infection. Other oral treatment options that have been shown to be effective for RVVC with azole-susceptible strains include suppressive therapy with ketoconazole (100 mg daily) (232) and with itraconazole (200 mg twice daily for one day each month) (286). However, because of liver toxicity associated with oral ketoconazole (148), other regimens are now preferred as maintenance therapy. For women with RVVC who prefer topical to oral drugs, clotrimazole (500-mg suppositories weekly or 200-mg suppositories twice weekly) is recommended (189), although the 500-mg formulation is no longer available in the United States. Alternatively, other forms of topical maintenance therapy can be considered, without data supporting the use of a specific topical formulation. Patients on no maintenance therapy have a recurrence rate of over 70% within the first 6 months after successful treatment of VVC (233), while a 40% to 50% recurrence rate after a 12-month cessation of maintenance therapy has to be anticipated (242). Non-*C. albicans*-related disease is less likely to respond to azole therapy (184). Vaginal boric acid, administered in a gelatin capsule at a dosage of 600 mg daily for 14 days, cures up to 70% of *C. glabrata* infections (238). Treatment with AmB suppositories (50 mg nightly for 14 days) is another option with minimal side effects that has shown to be successful in 70% of women with non-*C. albicans* VVC, mostly due to *C. glabrata*, that did not respond to azole treatment (197). Other alternatives include topical 17% flucytosine cream alone or in combination with 3% AmB cream administered daily for 14 days, albeit at considerable expense due to the high cost of flucytosine (189). Of note is that all the treatment options for non-*C. albicans* VVC need to be compounded.

**Probiotics and other alternative methods for treatment of RVVC.** Many women with RVVC turn to probiotics or alternative methods as adjunct or sole therapy to control their recurrences. Most probiotics, in oral or topical formulation, contain lactobacilli, which are felt to inhibit or reduce the growth of *Candida* in the vaginal tract. While some clinical trials support the effectiveness of certain lactobacilli, others do not, and most are limited by methodological problems (83). There are a number of other nonconventional methods available, but these have not been assessed in well-designed randomized clinical trials (275). One recently published randomized clinical trial showed that monthly oral itraconazole treatment was significantly more effective in preventing recurrent episodes of VVC than a homeopathic regimen and that an *L. acidophilus*-containing agent applied intravaginally did not add any benefit to itraconazole treatment alone (286).

## Treatment of Candiduria

The presence of yeast in the urine, whether microscopically visualized or grown in culture, must be evaluated in the context of the clinical setting to determine its relevance and make an appropriate decision about the need for antifungal therapy. Similar to the case for asymptomatic bacteriuria, there has been a revolving debate on whether and how to treat patients with candiduria (180). Several facts have to be taken into consideration. First, as outlined above, decreased survival of candiduric patients compared to matched control populations has been consistently reported. Second, large treatment trials with fluconazole have demonstrated that treatment clears only half of the patients successfully and has no impact on survival (241). Lastly, asymptomatic candiduria can resolve spontaneously or with catheter removal alone (241). High-risk patients can be treated with antifungal medication prophylactically. In neonatal ICU patients, especially those with low birth weight, fluconazole prophylaxis may prevent invasive candidiasis (111, 112), although another study concluded that mortality was similar among treated and untreated groups despite lower rates of colonization (135). In adult ICU patients, a recent large multicenter study could not exclude a relative benefit of fluconazole in up to a 32% difference in success (defined by the composite endpoint) between fluconazole and placebo recipients (224). However, the rates of invasive fungal infection in that study were low, and confidence limits were wide. In addition, their inclusion criteria required that the patients were febrile, and their outcome measurement constituted of four factors that made up a composite endpoint: resolution of the index fever, no emergent invasive fungal infection identified, no study medication treatment stopped for toxicity, and no use of alternative systemic antifungal medication. Other studies have reached different conclusions, but not all of them are generalizable to most ICU patients because they involve patients with very specific predisposing risk factors (100, 194).

Importantly, these studies did not report emergence of resistance. A concern with respect to overtreatment is that excessive treatment and prophylaxis may affect the overall microbiotome.

Fluconazole is the main drug used in candiduric adults and in neonates. Oral fluconazole therapy gives bioavailability of 90%, diffuses readily into all body sites, and is concentrated in the urine and skin (36, 37). The echinocandins have very few side effects but are poorly renally excreted (33), although there are a few animal studies and human case reports of successful treatment of persistent UTIs with resistant *C. glabrata* (6, 236). IDSA guidelines, however, do not currently recommend echinocandins for treatment of non-*C. albicans* candiduria because of very limited clinical data (189). Flucytosine, at a dosage of 25 mg/kg (rounded to the nearest 250 mg) orally four times daily, can also be used to treat cystitis (260). Because of its

marrow suppressive effects, patients have to be monitored. Concerns about the development of treatment-emergent resistance reported for flucytosine may be less relevant for candiduria because of the high concentrations of the drug in the urine and the relatively short duration of therapy.

Bladder irrigation with a suspension of amphotericin B is rarely considered. This treatment is used mostly in patients with refractory cystitis due to azole-resistant organisms, such as *C. glabrata* and *C. krusei*. Although irrigation resolves candiduria in 90% of patients (127), relapse is frequent and experts advise against this treatment modality (75). A recent meta-analysis on amphotericin B bladder irrigation, which included 213 studies and 377 patients, demonstrated a higher clearance of candiduria at 24 h after amphotericin B bladder irrigation than with fluconazole treatment (265). This finding stands in contrast to two randomized studies on 53 and 106 elderly patients, which concluded that both treatments had similar percentages of clearance (86a, 128). The latter study, however, found a lower overall survival in patients treated with amphotericin B irrigation (128). It is noteworthy that IDSA recommendations advise against the usage of liposomal amphotericin B as a first choice in pyelonephritis because of presumed low drug levels in renal tissue and treatment failure of *Candida* pyelonephritis in animals as well as a few treated patients (7, 269).

**Treatment of asymptomatic candiduria.** New updated IDSA guidelines (189) divide between asymptomatic and symptomatic candiduria, a distinction that as outlined could be challenging to make in certain clinical settings. If the candiduria is catheter associated, we often do not find the patients to be symptomatic or to exhibit leukocyturia (257, 258). The current guidelines recommend observation of asymptomatic patients and elimination of predisposing factors if feasible (133, 257). Specifically, removal of an indwelling catheter may be sufficient to eliminate candiduria without antifungal therapy. In contrast, asymptomatic patients with a high risk of dissemination, such as neutropenic patients and infants with low birth weight, should be treated with prolonged high-dose antifungal intravenous therapy. Also, urologic procedures enhance the risk for dissemination, and therefore candiduric patients should be treated before and after the procedure with fluconazole (dosage of 200 to 400 mg [3 to 6 mg/kg] daily). In selected cases (fluconazole-resistant non-*C. albicans* species), amphotericin can be administered (0.3 to 0.6 mg/kg daily). If indicated, imaging of the kidneys and collecting system to exclude abscess, fungus ball, or urologic abnormality is advised.

**Treatment of symptomatic candiduria.** Treatment depends on the disease manifestation. *Candida* cystitis can be treated orally (200 mg per day for 14 days). Pyelonephritis is also treated with 200 to 400 mg per day for 2 weeks. As outlined, other azoles or echinocandins may not be useful because of minimal excretion of active drug into the urine. Azole-resistant *Candida* strains, such as *C. glabrata*, *C. tropicalis*, or *C. krusei*, are treated with alternative regimens. Standard amphotericin at a dosage of 0.5 to 0.7 mg/kg daily can be used with or without flucytosine at a dosage of 25 mg/kg four times daily. Complicated emphysematous UTIs have been described, especially in diabetic patients. These infections require aggressive management and often surgical intervention, as they can be life-threatening (58, 74, 211, 252, 254, 279). Also, successful treatment of perinephric abscess usually consists of percutaneous or surgical drainage of the abscess (114).

**Treatment of other causes of candiduria.** *Candida* prostatitis and epididymo-orchitis are rare (23, 282) and usually require surgical drainage or other surgical debridement, in addition to antifungal therapy. Fluconazole is the agent of choice, but treatment recommendations are based on anecdotal data. Candidal bezoars or "fungus balls" in the urinary collecting system are described mainly in neonates (203). Aggressive surgical debridement is required in addition to systemic treatment with amphotericin (with or without flucytosine) or fluconazole (24, 55, 167). Debulking of the fungal mass and aggressive local irrigation with amphotericin and even streptokinase could be considered as an adjunct to systemic antifungal therapy if a percutaneous device provides direct access (17, 53, 227). Percutaneous nephrostomies can relieve the obstruction initially and also permit irrigation with antifungals (19). In some cases where irrigation via nephrostomy tubes failed, subsequent flank exploration and bilateral cutaneous calicostomies were performed and successfully eradicated persistent fungal disease (41). The patient's urinary tract was successfully diverted and the fungal balls eradicated. It is noteworthy that nonsurgical management of neonatal obstructive uropathy can also be successful and may constitute an alternative, especially in neonates (169).

Lastly, it is important to note that these recommendations are based largely on expert opinions and committees and are only scarcely backed by randomized controlled studies. In addition, these guidelines are not followed consistently by treating physicians (51). Especially since new data now indicate that candiduria is underdiagnosed, it is our opinion that treatment regimens and outcome should be revisited, and studies that define asymptomatic and symptomatic candiduria are warranted.

## CONCLUSIONS

As outlined in this review, genitourinary candidiasis is exceedingly common. Although *C. albicans* remains the main responsible species, non-*C. albicans* species are emerging, highlighting the importance of improved and reliable culture techniques. The different disease manifestations are distinct from each other and affect different risk groups, and thus treatment regimens and indications differ also. For candiduria the benefit and the indication of treatment is disputed. Despite its high incidence and clinical relevance, genitourinary candidiasis is understudied, and therefore important questions about pathogenesis and treatment guidelines remain to be resolved. Candiduria is associated with increased mortality, and genital candidiasis is associated with considerable morbidity. Given how many patients are affected, the psychological, medical, and socioeconomic impact of these diseases is likely greatly underestimated.

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