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Candida glabrata: Review of Epidemiology, Pathogenesis, and Clinical Disease with Comparison to *C. albicans*

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INTRODUCTION

Historically, *Candida glabrata* has been considered a relatively nonpathogenic saprophyte of the normal flora of healthy individuals, rarely causing serious infection in humans (57, 163). However, following the widespread and increased use of immunosuppressive therapy together with broad-spectrum antimycotic therapy, the frequency of mucosal and systemic infections caused by *C. glabrata* has increased significantly (65, 86, 90, 120, 143, 166, 179, 184). In fact, depending on the site of infection, *C. glabrata* is often the second or third most common cause of candidiasis after *C. albicans. C. glabrata* infections can be mucosal or systemic and are common in abnormal hosts (e.g., immunocompromised persons or those with diabetes mellitus) (53, 148, 149, 182). In contrast to other *Candida* species, *C. glabrata* is not dimorphic; consequently, it is found as blastoconidia both as a commensal and as a pathogen. *C. glabrata* infections are difficult to treat and are often resistant to many azole antifungal agents, especially fluconazole (65, 90, 167, 179). Consequently, *C. glabrata* infections have a high mortality rate in compromised, at-risk hospitalized patients.

Unfortunately, there have been relatively few investigations of *C. glabrata* compared to other *Candida* species. Although this infection is second or third in frequency after *C. albicans*, difficult to treat, and associated with a high mortality rate, publications to date on *C. glabrata* account for only a small percentage of published studies on medically important fungal infections. Very little is known about the virulence of *C. glabrata*, and virtually nothing is known about the host defenses directed against the organism. There are only two established animal models of experimental *C. glabrata* infections (systemic and vaginal) (24, 41). Therefore, studies to understand the pathogenesis of *C. glabrata* infections are sorely needed. This review discusses what is currently known about *C. glabrata* infections and includes specific comparisons to *C. albicans* wherever possible. Specific topics discussed include its biology,

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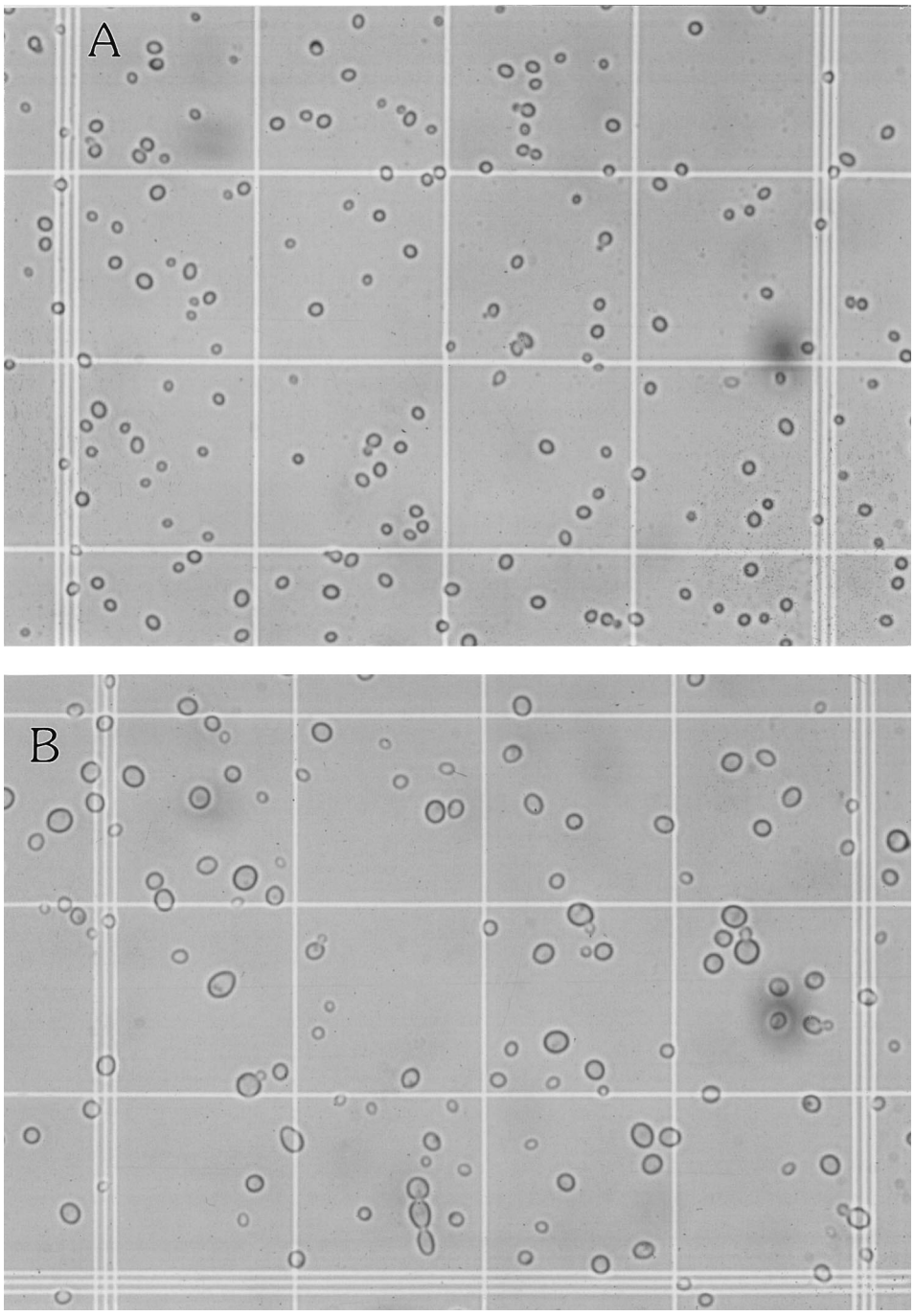

FIG. 1. Size differential of *C. glabrata* and *C. albicans*. Shown are wet-mount slide preparations of *C. glabrata* (A) and *C. albicans* (B) on a hemocytometer. Magnification, ×400.

epidemiology, pathogenesis, clinical perspectives, treatment, and antifungal resistance.

BIOLOGY

C. glabrata, together with other *Candida* species, belongs to the class Fungi Imperfecti, the order Moniliales, and the family Cryptococcaceae (91, 148). *C. glabrata* is a nondimorphic yeast that exists as small blastoconidia under all environmental conditions as a pathogen. In fact, *C. glabrata* is the only *Candida* species that does not form pseudohyphae at temperatures above 37°C. Figure 1 shows wet-mount preparations of *C. glabrata* and *C. albicans* at similar magnifications. It is clear that *C. glabrata* blastoconidia (1 to 4 μm) are considerably smaller than *C. albicans* blastoconidia (4 to 6 μm). On Sabouraud dextrose agar, *C. glabrata* forms glistening, smooth, cream-colored colonies which are relatively indistinguishable from those of other *Candida* species except for their relative size, which is quite small. On Chromagar, a relatively new agar that distinguishes different *Candida* species by color as a result

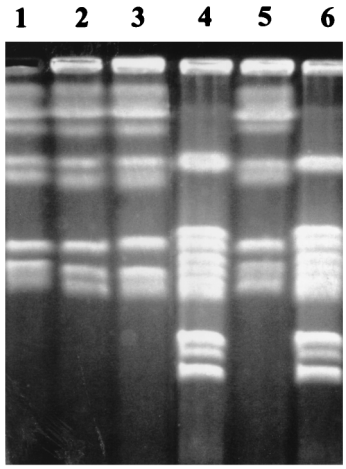

FIG. 2. CHEF of genomic DNA from representative isolates of *C. albicans* and *C. glabrata*. Lanes 1 to 3 and 5 are similar strains of *C. albicans*; lanes 4 and 6 are strains of *C. glabrata*.

of biochemical reactions, *C. glabrata* colonies appear pink to purple, in contrast to *C. albicans* colonies, which appear green to blue-green. A critical distinguishing characteristic of *C. glabrata* is its haploid genome, in contrast to the diploid genome of *C. albicans* and several other non-*albicans Candida* species (176). Finally, *C. glabrata* is distinguishable from *C. albicans* by its small-subunit rRNA (4).

Most medically important *Candida* species can be easily differentiated from one another by either established commercially available biochemical tests or molecular biology techniques. With the advent of molecular genetics, newer identification methods have emerged. These methods use comparative analysis of chromosomal DNA to identify *Candida* species from each other and also to delineate different strains within a species. These newer methods include restriction fragment length polymorphisms, pulsed-field gel electrophoresis, randomly amplified polymorphic DNA, and DNA probes (77, 79, 95, 170). By using contour-clamped homogeneous electric field gel electrophoresis (CHEF), a form of pulsed-field gel electrophoresis, chromosomal DNA from *C. glabrata* can be separated based on the different chromosomal molecular weights and thus can be subjected to electrophoretic karyotyping (EK). The EK pattern of *C. glabrata* generally produces 10 to 13 bands (79, 170). Depending on the EK patterns, *C. glabrata* can be classified into several different strain types. To date, 28 strain types have been formally described (170), although more than 70 different strains have been identified (168). In contrast, CHEF usually separates *C. albicans* chromosomal DNA into eight chromosomal bands, with more than 90 different strain types identified to date (168). Figure 2 shows the CHEF-derived DNA-banding patterns characteristic of *C. glabrata* and *C. albicans*.

The biochemical reactions of *C. glabrata* are also quite distinct. In contrast to *C. albicans*, which ferments and/or assimilates a number of sugars, *C. glabrata* ferments and assimilates only glucose and trehalose (91). In fact, this repertoire of sugar utilization is unique compared to the majority of *Candida* species and is used by several commercially available kits (API 20C, Uni-Yeast-Tek, and YeastIdent) to identify yeast to the level of genus and species.

Historically, *C. glabrata* was classified in the genus *Torulopsis* (91). The genus *Torulopsis* was described in 1894, while the genus *Candida* was not named until 1913. *C. glabrata* was originally placed in the genus *Torulopsis* due to its lack of pseudohypha production. However, in 1978, it was determined that the ability to produce pseudohyphae was not a reliable distinguishing factor for members of the genus *Candida* and it was proposed that *T. glabrata* be classified in the genus *Candida* (91). The incorporation of *T. glabrata* into the genus *Candida* required that the description relative to pseudohyphae for the genus *Candida* be changed from "pseudomycelial" to "pseudohyphae: absent, rudimentary, or well developed" (91). This change in nomenclature has taken considerable time to gain acceptance by the medical mycology community, and several publications still refer to *C. glabrata* as *T. glabrata*. Wherever possible, efforts should be made to use the contemporary nomenclature.

TABLE 1. Epidemiology of *C. glabrata* infection

Predominantly nosocomial (except vaginal)
Immunocompromised or debilitated host
Specific risk factors:
Prolonged hospitalization
Prior antibiotic use
Use of fluconazole
General use in hospital
Patient exposure
Hand carriage by hospital personnel
Often mixed fungal infection

EPIDEMIOLOGY

Candida species are ubiquitous organisms (115). An increasing incidence of fungal infections with *Candida* species has been noted in immunocompromised patients such as intensive-care, postsurgical, and neutropenic patients (7, 11, 14, 67, 90, 175). *Candida* species are most frequently isolated from the oral cavity and are detected in approximately 31 to 55% of healthy individuals (115). Colonization rates increase with severity of illness and duration of hospitalization (115, 170, 175). Historically, *C. albicans* accounted for 70 to 80% of the isolates recovered from infected patients. *C. glabrata* and *C. tropicalis* each accounted for approximately 5 to 8% of isolates, while other non-*albicans Candida* species occur only rarely (3, 7). However, more recent epidemiological data reveal a mycological shift from *C. albicans* to the non-*albicans Candida* species such as *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* (7, 90, 107, 180, 183, 184).

The changing patterns and the increasing incidence of disseminated *Candida* infection are also evident in a large autopsy series (11). The high mortality rate associated with bacterial infections has declined with the early administration of empirical antibiotics, while systemic fungal infections have become increasingly important in causing morbidity and mortality in immunocompromised patients. *Candida* is now the fourth most common organism recovered from blood cultures in hospitalized patients (7). *C. glabrata* has recently emerged as an important nosocomial pathogen, yet little is known about its epidemiology. Although *C. albicans* is the most common fungal species isolated from blood, *C. glabrata* currently ranks fourth among *Candida* species (third in patients who have undergone surgery) and is associated with an equally high mortality rate (51, 90, 181, 184). *C. glabrata* is of special importance because of its innately increased resistance to antifungal agents, specifically the azoles (49, 61, 174, 181, 184). The current epidemiological data for *C. glabrata* is summarized in Table 1.

A clear understanding of the epidemiology of *Candida* infection and colonization has been difficult because of a lack of

reliable typing systems to evaluate strain homology. Previous typing systems have relied on phenotypic differences within a *Candida* species, which may not reflect true strain differences (26, 71, 106). However, recent advances in the use of molecular techniques have enabled investigators to develop a typing system with greater sensitivity (26, 34, 70, 71, 106, 169, 172). Molecular typing of *Candida* by DNA fingerprinting involving various molecular techniques (restriction fragment length polymorphism, CHEF, and randomly amplified polymorphic DNA), has the capability to differentiate closely related strains which may have phenotypic similarities (26, 70, 79, 161, 169, 172).

Based upon epidemiological studies, it is apparent that humans are exposed repeatedly to *Candida* in food and other sources. However, the natural history of this commensal "normal" colonization over weeks, months, and years is poorly understood. Nevertheless, one may reasonably conclude that *Candida* colonization is almost universal. A feature common to colonized individuals is that the most frequent species are still *C. albicans*, and so far no unique strains of *C. albicans* or any non-*albicans Candida* species with specific gastrointestinal tract tropism have been identified. DNA typing of *Candida* strains obtained from AIDS patients with oral and esophageal candidiasis indicate an identical distribution frequency to those of isolates present in healthy subjects (12). This suggests that AIDS-associated candidiasis is not caused by unique or particularly virulent strains but probably results from defects in host defense mechanisms.

Until recently, most reports describing the epidemiology of nosocomial *C. glabrata* have been retrospective, and few studies have evaluated independent risk factors associated with nosocomial *C. glabrata* acquisition and subsequent infection. Knowledge of the epidemiology of fungal nosocomial colonization and infection with *C. glabrata* is, however, essential for the prevention of further spread as well as of nosocomial infection. In a recent study by Vazquez and colleagues (170), multivariate prospective case-control analysis along with molecular analysis of *C. glabrata* demonstrated that patients with new acquisition of *C. glabrata* had a longer duration of hospitalization (18.8 and 7.6 days, respectively; $P < 0.001$) and more frequent prior antimicrobial use (100 and 65%, respectively; $P < 0.001$) compared to patients from whom *Candida* species were not recovered during the study. These results are similar to the findings noted in earlier epidemiological studies of *C. albicans*, *C. lusitaniae*, and *C. parapsilosis* (138, 139, 172). Little is known about the hospital reservoirs of *C. glabrata*, but, as with *C. albicans*, probable sources include a complex interaction of environmental and human reservoirs (72, 172). The unique role of the hospital environment as a potential reservoir for *Candida* species is further suggested by findings in a recent study in which identical strains of *C. glabrata* were isolated from the environment before being newly acquired by patients admitted into a Bone Marrow Transplant Unit (170). Fungal organisms isolated from the inanimate hospital environment were previously considered to contribute little to nosocomial fungal infection. Although infecting strains can be cultured from environmental surfaces, it is believed that the environment becomes passively contaminated by organisms from patients (170, 172). Two studies have implicated carriage on the hands of hospital personnel as a possible source of an outbreak (75, 172). Thus, *C. glabrata* may be similar to *C. albicans* and other nosocomial pathogens that are acquired directly or indirectly from contaminated environmental surfaces. Previous understanding of the pathogenesis of *C. glabrata* colonization and infection assumed that the organisms responsible for disease were endogenously acquired exclusively from the patients' own flora.

The role of carriage by personnel in dissemination of *C. glabrata* remains to be clarified. Although *C. glabrata* is not frequently recovered from the hands of hospital personnel, transient carriage is suggested by its isolation on environmental surfaces in contact with hands (170). Perhaps more frequent culturing of the hands of personnel or the use of liquid media to recover yeasts may have improved the detection rates of *C. glabrata*. Proximity to a patient with infection or colonization increases the risk of nosocomial acquisition (170). As in earlier studies (124, 172), the results of longitudinal cultures showed that 75% of patients generally carried the same strain type of *C. glabrata* over time (170), with minimal strain diversity among individual patients. This finding is significantly different from the results described for the nosocomial acquisition of *C. albicans*, in which there was considerable strain diversity (172). Moreover, in this study, 71% of patients with positive *C. glabrata* cultures had more than one *Candida* species isolated. The most frequent combination was *C. glabrata* and *C. albicans*, which was found in approximately 70% of the patients. This again is in contrast to the findings previously described for *C. albicans*, which showed that only 39% of patients with *C. albicans* had more than one *Candida* species identified (175). Finally, unlike *C. albicans*, *C. glabrata* has not been recovered from the food provided to hospitalized patients, potentially contributing to the lack of identifiable *C. glabrata* strain diversity.

In conclusion, these studies suggest that nosocomial acquisition of *C. glabrata* is not uncommon and may be due to exogenous acquisition. In addition, two major risk factors associated with *C. glabrata* colonization are prolonged duration of hospitalization and prior antimicrobial use. Further prospective studies are sorely needed to define more clearly the reservoirs of infection, as well as the mode of transfer and measures for preventing the spread of infection.

PATHOGENESIS

In this section, although very little has been studied, we discuss what is currently known about virulence factors of *C. glabrata*, host defense against this organism, and established experimental animal models of *C. glabrata* infections.

Virulence

The relatively nonpathogenic nature of *C. glabrata* in animal models (24, 41, 145) suggests that it has few virulence attributes. However, the high mortality rate and the rapidity of the spread of disease would argue to the contrary. The fact is that few studies have been conducted on virulence of *C. glabrata*. In contrast, *C. albicans* has several known virulence factors contributing to its pathogenicity that include adherence to epithelial and endothelial cells, proteinase production (17, 135), hypha and pseudohypha formation (114, 154), phenotypic switching (156), phospholipase production (5, 73), and antigenic modulation as a result of pseudohypha formation (25). If *C. glabrata* is low in virulence, the lack of hypha formation may be a contributing factor. Indeed, hypha formation is a recognized means of increased adherence and tissue invasion by *C. albicans* as well as a means of increasing proteolytic enzyme elaboration and antigen modulation (114).

Proteinase production by *C. albicans* is associated with pathogenicity (17, 135). For example, virulent *C. albicans* isolates often produce aspartyl proteinase. These isolates are more pathogenic in a variety of animal models of experimental

Candida infections (17, 23). Although little is known of proteinase production by *C. glabrata*, a single study has shown that isolates of *C. glabrata* are at least capable of proteinase production, but the type of proteinase was not specified (19).

Adherence is an extremely important virulence factor, although the actual adherence property may be compounded by other virulence properties. For example, cell surface hydrophobicity (CSH), which is affected by environmental factors, can affect specific adherence based upon interaction of adhesin receptors. In a study with limited numbers of *C. glabrata* isolates tested, *C. glabrata* was shown to have comparable CSH to *C. albicans* (85). Interestingly, however, while the CSH of *C. albicans* was extremely sensitive to specific growth conditions, numerous isolates of *C. glabrata* were relatively insensitive to those same growth conditions (60), suggesting that *C. glabrata* is not as sensitive or as influenced by environmental factors. In comparative in vitro assays of adherence to vascular endothelium, while *C. albicans* was by far the most adherent species, *C. glabrata* was the least adherent, alone with *C. parapsilosis* and *C. kefyr*, behind *C. tropicalis* and *C. krusei* (84). Moreover, while *C. albicans* is recognized avidly by monoclonal antibodies to β_2 integrins (adhesin receptors), binding to *C. glabrata* by the same antibodies was undetectable, as was binding to *C. parapsilosis* and *C. krusei*. These results suggest that *C. glabrata* may not express these specific adhesins and thus would have a disadvantage in adherence (8). The presence of fibronectin, and laminin receptors, fibrinogen-binding proteins, and mannoprotein adhesins are also considered important means of adhesion to endothelial and/or epithelial cells (reviewed in reference 69). While extensive work has been performed on surface ligands of *C. albicans*, nothing is known about these receptors and proteins on *C. glabrata*. It will be important to reexamine many of the parameters from earlier studies, together with a number of new parameters, by using current clinical *C. glabrata* isolates obtained from patients with fulminant candidiasis.

Extracellular membrane-damaging phopholipases are considered virulence factors for *C. albicans* (5, 73). Although these enzymes have not been studied extensively, phospholipase A and B and lysophospholipase-transacylase are produced by virulent but not avirulent (commensal) strains of *C. albicans*. These phospholipase-producing strains also adhered most strongly to epithelial cells. Furthermore, the production of these phospholipases by clinical isolates correlated with pathogenicity and was predictive of mortality in animal models (5, 73). Phospholipase activity has not been studied in *C. glabrata*.

Another virulence factor of *C. albicans* is specific phenotypic instability, which allows strains to switch colony phenotype without affecting the identifiable genotype; this is termed "phenotypic switching" (155, 156). Although phenotypic switching was studied largely as an in vitro phenomenon, there is some evidence of in vivo phenotype switching and an association of switched phenotypes with virulence. Switching of phenotypes in clinical *C. albicans* isolates from women with recurrent *C. albicans* vaginitis has been reported (158). Recently, it was determined that phenotype switching does occur in *C. glabrata* (157). It is interesting that such a phenomenon would occur in nondimorphic organisms as well as in haploid organisms. Although the relationship of this *C. glabrata* phenotype switching to virulence is unknown, it may enhance virulence and play a role in causing symptomatic infection.

Host Defense

Little is known about host defense against *C. glabrata*. In contrast, considerable work has been described on host defenses against *C. albicans*. As a result, we now have a fairly comprehensive understanding of the dominant host defense and protective mechanisms against invasive *C. albicans* infection, both superficial and systemic, but we know little about *C. glabrata* infection. With respect to defense against systemic *C. albicans* infections, clinical observations and experimental studies suggest that polymorphonuclear leukocytes are the predominant cell type that protects against candidemia and systemic candidiasis (32, 35, 66, 114). Clinically, this is supported by the fact that neutropenic patients are particularly susceptible to systemic *C. albicans* infections. In addition, it has been shown in an animal model that T cells may be of some significance against systemic *C. albicans* infections. Specifically, studies in mice have shown that a Th1-type response characterized by the cytokines interleukin-2 (IL-2), gamma interferon, and IL-12 is associated with protection against systemic infection whereas Th2-type responses characterized by the cytokines IL-4, IL-5, and IL-10 and antibody production (immunoglobulin A [IgA] and IgE) is associated with susceptibility to systemic infection (134). T cells and cell-mediated immunity (CMI), on the other hand, form the predominant host defense mechanism against mucosal *C. albicans* infection. This comes from both clinical observations (a high incidence of mucosal candidiasis in patients with reduced CMI) and clinical and experimental studies showing the critical role of T cells in protection against *C. albicans* mucosal infections (i.e., chronic mucocutaneous candidiasis and gastrointestinal candidiasis) (10, 15, 81, 82, 114). Historically, vaginal infections were included in the mucosal infections affected by T-cell host defense mechanisms. However, recent studies suggest that if T cells are indeed important, it is the local rather than the systemic T-cell response that is protective against vaginal *C. albicans* infection. This conclusion is based in part on studies in an experimental animal model of vaginitis as well as on clinical studies in women with recurrent vulvovaginal candidiasis (40, 43–46). In addition, although controversy abounds, properly controlled clinical studies suggest that *Candida* vaginitis is not more common in human immunodeficiency virus (HIV)-infected women and, if observed, does not correlate with decreased CD4 cell counts (20, 74, 131, 177). Recent studies suggest that innate resistance may also be critical for protection against vaginal *C. albicans* infections (160). Although antibodies are readily induced from exposure to *C. albicans*, it remains unclear if they play a protective role against *C. albicans* infections. Although several authors have concluded that they are nonprotective (101, 133), there are reports showing that specific antibodies protect against experimental systemic or vaginal *C. albicans* infections (58, 102, 103). Clinical experience, however, shows that individuals with B-cell deficiencies do not have increased susceptibility to *C. albicans* infection (133).

Since *C. glabrata* is a commensal organism similar to *C. albicans*, there are likely to be normal host mechanisms that effectively control *C. glabrata*, holding it in check and suppressing the expression of its pathogenic properties, thereby preventing infection. However, the relatively low pathogenicity of *C. glabrata* compared to *C. albicans* in animal models (reviewed below) suggests that control of *C. glabrata* may not require mechanisms that are as stringent as that required to hold *C. albicans* in check. Nevertheless, the increased prevalence of *C. glabrata* infections in immunocompromised individuals indicates that some level of host defense does indeed exist. The interaction of *Candida* species with endothelial and epithelial cells has recently taken an immunological twist in addition to a simple adherence phenomenon. We recently showed that epithelial cells inhibit the growth of *C. albicans* in vitro (160), and Filler et al. have shown that endothelial cells

phagocytize *C. albicans* (47). Unfortunately, *C. glabrata* did not induce endothelial-cell phagocytosis (47), suggesting that this endothelial-cell activity may be species specific or restricted to *C. albicans* alone. However, it remains possible that both conventional and unconventional immune cells play some role in innate and/or acquired host defense against *C. glabrata* infection.

There has been only one formal clinical study that examined host defenses in patients with *C. glabrata* infections (105). In this German study, humoral and innate cellular defenses were examined in women with either *C. glabrata* or *C. albicans* vaginitis. A total of 14 women with *C. glabrata* vaginitis and 20 and 42 women with acute or chronic *C. albicans* vaginitis, respectively, were tested. The responses were compared to those in 77 control women. For each woman, secretory IgA (sIgA), IgA, and numbers of granulocytes and macrophages in vaginal secretions and IgA in blood were tested. For each parameter, few differences were detected with respect to the controls. In fact, the only difference in the entire study was in women with *C. glabrata* vaginitis, who showed a slight, but significantly lower level of sIgA in vaginal secretions (105). However, it is unclear what proportion of the IgA measured was *C. glabrata* or *Candida* specific. Also noted in the women with *C. glabrata* vaginitis was a lack of inflammation compared to those with *C. albicans* vaginitis. While no clear pattern of local or systemic innate or humoral immune deficiency was observed in women with *C. glabrata* vaginitis and although local or systemic T-cell function in response to *C. glabrata* was not tested, it would appear that identification of immunological deficiencies and dysfunctions in *C. glabrata*-infected women may prove to be as difficult as it has been for those with *C. albicans* vaginitis (42, 44, 48, 105).

In the absence of other formal studies, there have been clinical observations that provide some indication of what may be important for host defense against mucosal or systemic *C. glabrata* infections. The incidence of *C. glabrata* mucosal or systemic infections in cancer patients (182), transplant recipients (184), and AIDS patients (37, 140, 179), in whom T-cell function is impaired, suggests that T cells may be important for protection of at least some tissues against *C. glabrata* infection. Additionally, histological examination of tissues infected with *C. glabrata* has shown relatively mild infiltrates of lymphocytes, macrophages, and neutrophils (61) compared to that observed in *C. albicans* infection. In contrast, there are no known reports of increased *C. glabrata* infections in patients with B-cell deficiencies, again suggesting that antibodies are not critical to protection against *C. glabrata* infections.

In studies comparing antigens of *C. glabrata* to those found in other *Candida* species, specific antigens appear to be common across several *Candida* species (13, 109). Certain antibodies produced against *C. albicans* recognize *C. glabrata* as well as other *Candida* species. Specifically, antibodies reacting with antigen 6 of *C. albicans* serotype A react with *C. glabrata* as well, suggesting that antigen 6 is conserved between the two species (109). Additionally, Cutler and coworkers (13) have reported an antibody produced against *C. glabrata* that also cross-reacts with other *Candida* species. These results suggest that protective immunity against *Candida* species, specifically *C. albicans*, may be capable of providing a level of protection against *C. glabrata* infections as well. This could potentially include any form of innate resistance (polymorphonuclear leukocytes, macrophages, and natural killer cells) or acquired CMI (T cells) in addition to humoral responses (B cells and antibodies).

Our laboratory has performed a limited number of experiments involving immune system reactivity to *C. glabrata*. In a limited number of tests performed with human peripheral blood lymphocytes, we recently found that human peripheral blood lymphocytes respond in vitro to heat-killed *C. glabrata* in a manner similar (approximately 80 to 85% in magnitude) to that observed for *C. albicans* (38). Thus, normal healthy adults appear to be sensitized to *C. glabrata* with demonstrable cell-mediated responsiveness, although we recognize that such responses may be the result of cross-reactive antigens on *C. glabrata* recognized by *C. albicans*-specific cells. In an animal model, we found that nonobese diabetic (NOD) mice infected vaginally with *C. glabrata* did not respond by developing delayed-type hypersensitivity to *C. albicans* culture filtrate antigen (38) whereas mice used in the experimental *C. albicans* vaginitis model (CBA/J mice) readily respond to *C. albicans* culture filtrate antigen by developing delayed-type hypersensitivity (39). This data suggests that a vaginal *C. glabrata* infection does not induce a systemic CMI response that is cross-reactive or responsive to *C. albicans* antigen. However, it is not known whether this is due to the lack of cross-reactivity between *C. glabrata* and *C. albicans*, the lack of induction of *C. glabrata*-specific CMI, or the inability of NOD mice to mount an effective T-cell response. There have been inconsistent results with the NOD mice regarding in vitro T-cell reactivity. In one study, draining lymph node cells from NOD mice infected vaginally with *C. glabrata* responded to both heat-killed *C. glabrata* and heat-killed *C. albicans* as detected by lymphocyte proliferation, whereas in another study, the lymph node cells did not respond to either particulate antigen (38). Although additional studies should be performed, if indeed *C. glabrata*-infected mice do generate *Candida*-specific T-cell responses in the draining lymph nodes, there appears to be some level of cross-reactivity between the responses to *C. glabrata* and *C. albicans*. However, the critical experiments involving the lymph node responses to *C. glabrata* in *C. albicans*-infected mice have not been performed. The predominant response of draining lymph node cells in such infected mice to *C. albicans* antigen is a Th1-type response characterized by the production of IL-2 and gamma interferon (110). Finally, understanding the important host defenses against *C. glabrata* will require controlled studies conducted in animal models of systemic and mucosal *C. glabrata* infections.

Animal Models

Historically, there has been little interest in developing animal models of *C. glabrata* infection. Even now, despite the emergence of both systemic and mucosal *C. glabrata* infections, there are still only a few established animals models. The relative lack of pathogenicity of *C. glabrata* may have hampered the development of such models, and it continues to do so. Currently, there are two established murine models of *C. glabrata* infections, systemic and vaginal (24, 41). For each model, steps have had to be taken to either manipulate the mice or identify a strain of mouse particularly susceptible to infection. In the systemic model, with several clinical isolates of *C. glabrata*, mice had to immunosuppressed with 5-fluorouracil (150 mg/kg) intravenously or subjected to gamma irradiation with 450 to 550 rads to achieve a sustained infection for 7 days (24). The smallest inoculum required to achieve an infection in these mice was 10^8 blastoconidia. This is approximately 3 to 4 log units higher than that which is lethal for immunocompetent mice inoculated systemically with *C. albicans*. In infected mice, a *C. glabrata* organ burden was detectable in the kidneys and spleen 7 days after inoculation. Since the focus of the study was to test various antimycotic treatment regimens during the course of a vigorous infection, a kinetic study of the organ

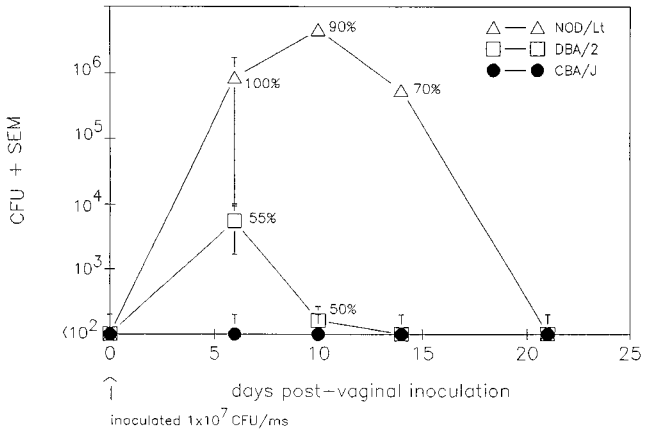

FIG. 3. Experimental *C. glabrata* infections in mice with intermediate (CBA/J) and high (DBA/2) susceptibilities to *C. albicans* systemic infection and in NOD/Lt mice. Data points represent mean CFU ± standard errors of the mean (SEM) in animals with positive cultures only (the percentage of animals with positive cultures is shown). Reprinted from reference 41 with permission of the publisher.

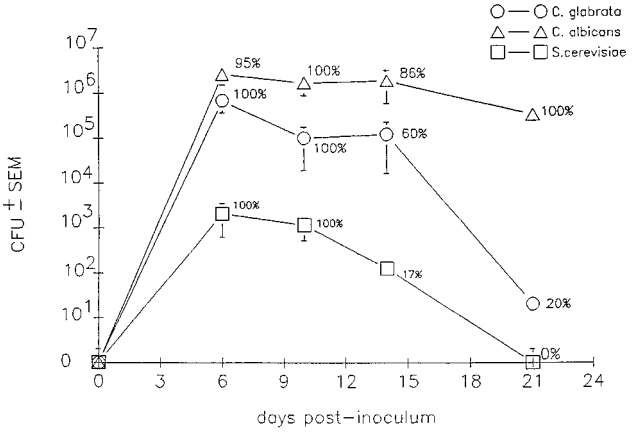

FIG. 4. Comparative analysis of *C. glabrata*, *C. albicans*, and *S. cerevisiae* vaginal fungal burden in NOD mice. Data points represent mean CFU ± SEM for animals with positive cultures (the percentage of animals with positive cultures is shown) following intravaginal inoculation with 1×10^7 blastoconidia of *C. glabrata* or *S. cerevisiae* or 5×10^5 blastoconidia of *C. albicans*. Reprinted from reference 41 with permission of the publisher.

fungal burden was not performed although the authors stated that lethality was not observed. Thus, survival was obviously not a parameter for consideration in the studies. In any event, the kidney and spleen fungal burden was quite high in many animals (10^4 to 10^8 CFU/organ), although the range of CFU per organ within a group of animals was large. Thus, the organ burden in *C. glabrata*-infected mice was comparable to that detected in *C. albicans*-infected mice (43); however, one should recall that the *C. glabrata*-infected mice were immunosuppressed. Moreover, it is notable that experimental *C. glabrata* infections are generally not lethal in animals. From this, one can appreciate the differences in relative pathogenicity between *C. albicans* and *C. glabrata*. While lack of lethality in experimental studies does not match the high mortality often seen in clinical cases of *C. glabrata* infection, one must recognize that the clinical experience is a reflection of the advanced state of debilitation of patients who become infected with *C. glabrata*. Clearly, more studies of the kinetics of the model must be performed to better understand the progression of infection. Although a section in this review is devoted to treatment of *C. glabrata* infections, the results of this systemic-infection model are consistent with clinical experience, in that amphotericin was most efficacious while fluconazole was generally ineffective. Moreover, a lack of correlation between in vitro susceptibility tests and in vivo efficacy was often evident (24, 41).

A recent report describing an increase in *C. glabrata* vaginal infections (151) emphasized the need to develop a vaginal model of *C. glabrata* infection. In particular, models of *C. glabrata* mucosal infections had been difficult to establish. In one report, an oral *C. glabrata* infection in rats could not be achieved (145). Our laboratory attempted to develop an experimental model of vaginal *C. glabrata* infection to complement our model of vaginal *C. albicans* infection (39). This also proved difficult. Preliminary experiments with the mouse strain used for *C. albicans* vaginal infection (immunocompetent CBA/J mice) showed no detectable *C. glabrata* vaginal burden as early as 6 days following an intravaginal inoculum in spite of using multiple clinical *C. glabrata* isolates and pseudoestrus conditions (required to achieve a vaginal *C. albicans* infection) (41). Similarly, a low detectable vaginal fungal burden was observed in DBA/2 mice, which are highly susceptible to systemic *C. albicans* infection (99). In contrast, nonobese diabetic (NOD/Lt) mice were susceptible to *C. glabrata* vaginal infection (Fig. 3) (41). In comparison to *C. albicans* infections, although a higher inoculum of *C. glabrata* was routinely used (1×10^7 blastoconidia) than that of *C. albicans* (5×10^5 blastoconidia), inocula as low as 5×10^5 blastoconidia were capable of establishing *C. glabrata* infections. The infection was sustained for 14 days at high titers and became resolved in most animals by 21 days. The vaginal titers of *C. glabrata* at 6 to 14 days postinoculum ($>10^6$ CFU) were higher than those commonly observed in *C. albicans*-infected mice (10^4 to 10^5 CFU) (39) and persist in pseudoestrus-treated mice for 8 weeks or more (39). We next examined how NOD mice could support vaginal infections caused by other fungal species, namely, *C. albicans* (highly virulent) and *Saccharomyces cerevisiae* (low virulence). Intravaginal inoculation with *C. albicans* resulted in extremely high titers of *C. albicans* ($>10^6$ CFU) and a surprising 20% mortality rate, although no dissemination of the organism could be detected (kidney dysfunction was suspected as the cause of death). Animals inoculated with *S. cerevisiae* had low but detectable titers of vaginal fungal burden ($<10^3$ CFU) early postinoculum (days 6 to 10), with the majority of animals resolving the infection by 14 days (Fig. 4). Another interesting feature of the *C. glabrata* vaginal infection in NOD mice was the relative lack of a requirement for pseudoestrus to acquire a sustained vaginal infection with either *C. glabrata* or *C. albicans*. Although the rates of infection were generally greater in pseudoestrus-treated mice, the vaginal fungal burdens were comparable in pseudoestrus-treated or and nontreated mice. This observation is in keeping with a clinical observation of *C. glabrata* being frequent in postmenopausal women developing *Candida* vaginitis (150).

Since it is difficult in animal models of vaginitis to determine whether a state of colonization or infectivity is achieved in the absence of measurable signs and symptoms of inflammation (and more difficult for the non-hypha-producing *C. glabrata*), there is nevertheless considerable evidence that the *C. glabrata*-inoculated animals were indeed infected. First, NOD mice had high titers of vaginal fungal burden whereas other murine strains did not. Second, there was a lymphoid cell-like

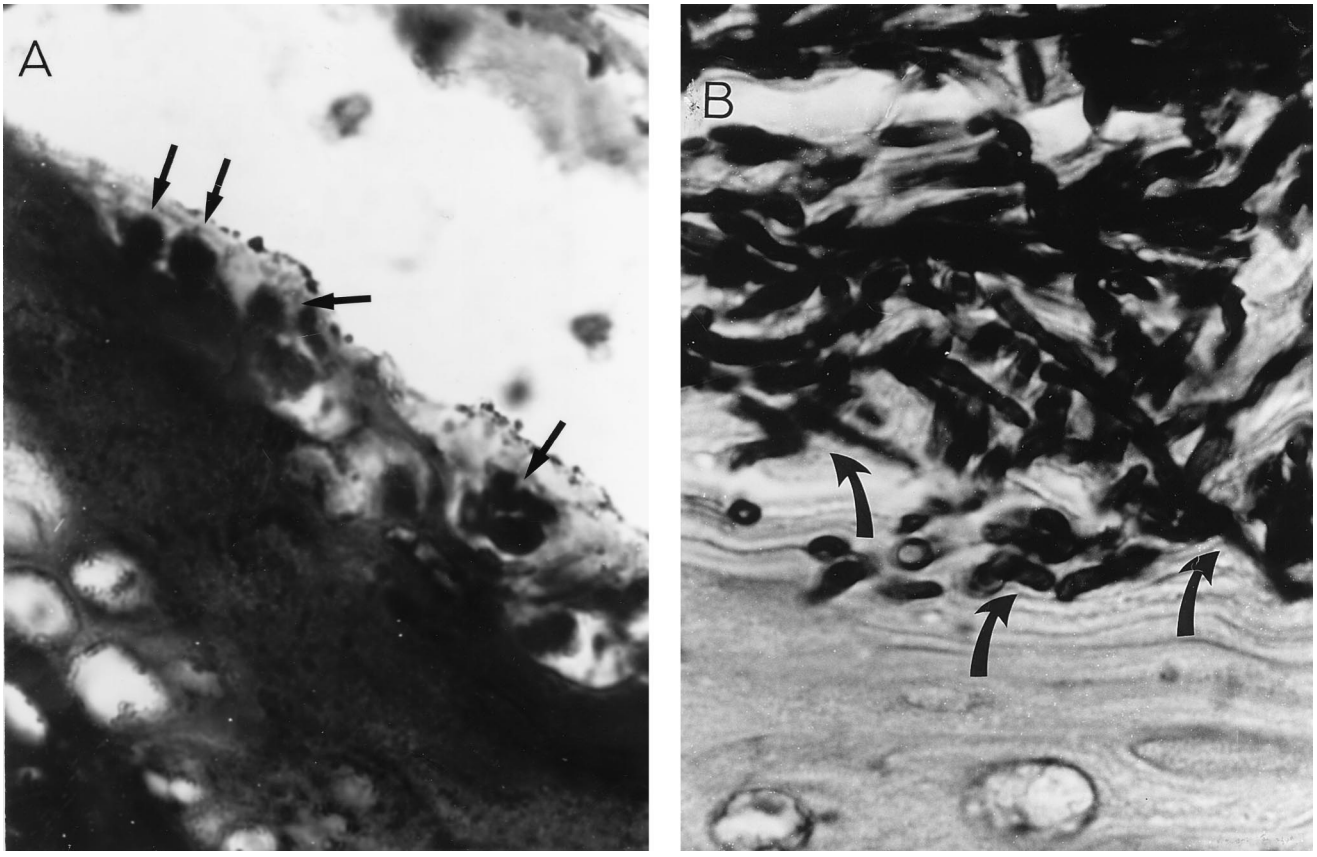

FIG. 5. Histopathology of vaginal tissue from estrogen-treated NOD mice inoculated with *C. glabrata* (A) and *C. albicans* (B). Arrows represent blastoconidia or hyphae. Magnification, ×100. Reprinted from reference 41 with permission of the publisher.

cellular infiltrate in the lavage fluid of *C. glabrata*-infected similar to that observed in *C. albicans*-infected mice. Third, histopathologic sections of vaginal tissue showed the presence of *C. glabrata* blastospores in epithelial vacuole-like vesicles and not simply lying at the epithelium (Fig. 5). Figure 5 also shows how *C. albicans* presents as predominantly hyphae superficially associated with the epithelium during an infection. Thus, these results show that NOD mice will be useful in studying the pathogenesis and host response during vaginal *C. glabrata* infections, as well as in developing strategies to treat the infection pharmacologically.

The use of NOD mice as a diabetic model was an interesting caveat to these studies. The model was originally conceived based on the high susceptibility of women with diabetes mellitus to *C. glabrata* and *C. albicans* vaginitis (53, 125, 149, 151). However, the NOD mice that were susceptible to the vaginal *C. glabrata* infection were not yet hyperglycemic. In fact, these mice do not achieve hyperglycemia until at least 12 weeks of age (80). The animals used in the named study were 7 to 10 weeks of age, and in our hands the NOD mice did not become hyperglycemic until 22 weeks of age. This susceptibility of NOD mice to *C. glabrata* vaginal infections before the onset of hyperglycemia prompted us to test the congenic insulitis-resistant strain of mice (NOR/Lt) for susceptibility to vaginal *C. glabrata* infection. Interestingly, the NOR mice were resistant to the vaginal infection (41). These results suggested that NOD mice may be susceptible to *C. glabrata* vaginal infection, not by virtue of a state of hyperglycemia but simply by their genetic susceptibility to diabetes mellitus. On the other hand, CBA/J mice made diabetic by exogenous treatment with streptozocin became susceptible to *C. glabrata* vaginal infection and NOD mice similarly treated had higher rates of infectivity (38). Certainly, more studies are required to better understand the factors that contribute to the susceptibility to *C. glabrata* vaginal infection. However, this experimental model of *C. glabrata* vaginitis provides an opportunity to study the pathogenesis of *C. glabrata* vaginal infections, as well as to dissect the genetic issues related to susceptibility to infection.

CLINICAL SPECTRUM OF INFECTION

Superficial Infections

Symptomatic mucosal candidiasis arises in subjects who are colonized with *Candida* and who are predisposed by illness or have a dysfunction or local reduction in host resistance, thereby promoting an overgrowth of their own indigenous yeast flora. The most common mucosal infections include oropharyngeal, esophageal, and vaginal candidiasis. Although *C. albicans* remains the species responsible for the overwhelming majority of infections in HIV-positive and negative patients (115, 152, 162, 164), there are an increasing number of case reports describing the recovery of *C. glabrata* from the mucosal surfaces of immune compromised patients. The actual rate of symptomatic oropharyngeal candidiasis (OPC) due to *C. glabrata* is difficult to determine since this species is rarely isolated alone and is often coisolated with *C. albicans*. In antifungal treatment trials involving HIV-positive patients, the recovery

TABLE 2. Agents available for treatment of OPC and esophageal candidiasis

Drug	Form	Strength	Use
Topical			
Nystatin	Vaginal tablet	100,000 U	Dissolve one tablet 3 times daily
Nystatin	Pastille	200,000 U	Dissolve one or two pastilles 4 times daily
Nystatin	Suspension	100,000 U	5-ml swish and swallow 4 times daily
Clotrimazole	Oral troche	10 mg	Dissolve one troche 5 times daily
Amphotericin B	Suspension	1 mg/ml	1-ml swish and swallow 4 times daily
Systemic			
Ketoconazole	Tablet	200 mg	Once daily
Fluconazole	Tablet	100 mg	Once daily
Fluconazole	Intravenous	5–10 mg/kg	Once daily
Itraconazole	Capsule	100 mg	200 mg daily
Itraconazole	Solution	10 mg/ml	10–20 ml 2 to 4 times daily

of non-*albicans Candida* species is generally less than 10% of all isolates recovered, with *C. glabrata* making up less than 5% (55, 122, 173). However, subjects in these treatment studies are often selected, while patients with advanced disease, who are likely to be infected with resistant strains, are excluded, resulting in an underestimation of the frequency of *C. glabrata* infection. Moreover, in several of the antifungal treatment trials for fluconazole-refractory OPC in AIDS patients, the incidence of *C. glabrata* producing OPC was less than 10% (16, 121). In the HIV-seronegative population, the occurrence of OPC and esophageal candidiasis due to *C. glabrata* is rare. Data are still incomplete, because only a few small studies have attempted to investigate the incidence of non-*albicans Candida* species as a cause of OPC and esophageal candidiasis (49, 140). At present, it is unclear why the incidence of mucosal candidiasis due to *C. glabrata* is so low. Perhaps studies evaluating the virulence factors of *C. glabrata* involved in the attachment and colonization of mucosal surfaces would shed some light on this important issue.

There continues to be considerable controversy about whether *C. glabrata*, as part of a mixed fungal culture with coexistent *C. albicans*, actually contributes to the development of OPC. Many investigators consider that *C. glabrata* functions as an innocent bystander only and that therapy should be based upon susceptibility of the coexistent *C. albicans* (140). While *C. albicans* is undoubtedly the more virulent, frequent, and dominant pathogen, *C. glabrata* is occasionally found as the single and only clinical species isolated in AIDS patients with OPC. Accordingly, while directing therapy against *C. albicans* in mixed infections, especially those not responding to appropriate therapy, it is prudent not to ignore *C. glabrata* in mixed infections.

Oropharyngeal. (i) Clinical manifestations. Several clinical forms of OPC exist; the most common and widely recognized is acute pseudomembranous candidiasis, commonly referred to as thrush. OPC can also occur in an erythematous form that is often asymptomatic. OPC is often the first manifestation of HIV infection (21, 56, 147), with approximately 80 to 90% of patients with AIDS ultimately developing OPC at some stage during their disease progression (28).

(ii) Management. Numerous antifungal agents are available for the treatment of OPC, esophageal and vaginal candidiasis (Table 2). Since the comparative efficacy of the antifungal agents has not been established in infections due to *C. glabrata*, the choice, dosage, and duration of treatment have not been well established in patients and remain somewhat controversial. Antimycotic efficacy and response time are inferior in the HIV-positive population to those in cancer patients. To date, most of the clinical trials contained few patients with OPC caused by *C. glabrata* alone. Thus, the efficacy of these antifungal agents for OPC due to *C. glabrata* is largely unknown. Azoles have replaced the topical polyene agents for the treatment of oral candidiasis in most circumstances. Accordingly, azole therapy for OPC due to *C. glabrata* is also extrapolated from the data accumulated from the numerous studies performed on OPC due primarily to *C. albicans* (Table 2).

The newer triazoles, itraconazole and fluconazole, which have markedly improved efficacy and safety profiles, have become extremely popular, especially for HIV and AIDS patients with severe OPC (29, 59, 87, 108, 111). Fluconazole (50 to 100 mg daily) has been studied in several open, placebo-controlled and double-blinded comparative studies versus clotrimazole or ketoconazole (59, 87, 108). Studies indicate that while clinical recovery is achievable in most patients treated, mycological cure is more difficult to attain. Additionally, most of the isolates recovered from study patients were *C. albicans*, with only a few isolates being identified as *C. glabrata*.

Itraconazole is a newer triazole antifungal with a broad spectrum of activity. Like the other azoles, it has a similar mechanism of action, acting by inhibiting the synthesis of fungal ergosterol. However, unlike fluconazole, it has in vitro activity against many of the non-*albicans Candida* species, specifically *C. glabrata* and *C. krusei*. In a recently completed prospective randomized trial involving HIV-positive or AIDS patients with OPC, itraconazole solution (200 mg/day) was compared to fluconazole (100 mg/day), both given for 14 days. The results revealed that the oral solutions of itraconazole and fluconazole were equivalent for most efficacy parameters. The clinical response rate was 97% for itraconazole and 87% for fluconazole, with few adverse events in both groups. Unfortunately, even anecdotally there is little data on OPC due to *C. glabrata* as a single pathogen or with *C. albicans* functioning as a contributory pathogen in a mixed infection in which specific anti-*C. glabrata* therapy was found to be effective when the anti-*C. albicans* regimens have failed.

Esophageal. (i) Clinical manifestations. *Candida* species are the most common cause of esophagitis, and after the oropharynx, the esophagus is the most common site of gastrointestinal candidiasis. The prevalence of *Candida* esophagitis has increased mainly because of the increased frequency during AIDS. Approximately 10 to 15% of AIDS patients will suffer from *Candida* esophagitis during their disease progression (28).

Candida is frequently cultured from the esophageal surface and reaches the esophagus in oral secretions. *C. albicans* is the species implicated in the majority of patients with esophagitis;

rarely is *C. glabrata* or any other *Candida* species recovered from esophageal samples. As with OPC, any *C. glabrata* strain recovered from esophageal surfaces is generally coisolated with *C. albicans*. However, in contrast to oral candidiasis, even less is known about host and yeast factors operative in the pathogenesis of esophageal candidiasis, and experimental models have not been established. Esophageal candidiasis in HIV-positive patients may be the first manifestation of frank AIDS.

(ii) Management. As stated above, all of the clinical efficacy studies evaluating antifungal agents for esophageal infection were performed on *C. albicans*. Therefore, as with most strategies used to treat infections due to *C. glabrata*, we tend to extrapolate the data acquired from studies involving *C. albicans*.

Oral and intravenous fluconazole treatments have now become an integral part of the management of *Candida* esophagitis. Oral fluconazole enjoys a superior safety profile compared to ketoconazole and has superior gastric absorption; when necessary, fluconazole can be given intravenously.

In a recently published trial by Wilcox et al., patients treated with oral itraconazole solution at a dose of 200 mg/day had a rate of clinical response comparable to that of patients treated with 100 mg of fluconazole per day (94 and 91%, respectively) (178). The mycological cure rates for this study was also similar, 92% for itraconazole and 78% for fluconazole.

Although used extensively in the pre-azole era for the more severe forms of esophagitis, therapy with an intravenous solution of amphotericin B is now used primarily in the azole-refractory cases. Low-dose intravenous amphotericin B, using either 0.15 to 0.3 mg/kg/day or 10 to 20 mg/day for 10 days, is often sufficient for moderate disease caused by *C. albicans* (9, 104), but with azole-refractory esophagitis, higher doses (0.5 to 0.7 mg/kg/day) are necessary.

Vulvovaginal. (i) Clinical manifestations. The majority of women with *Candida* vaginitis suffer from uncomplicated vaginitis characterized by sporadic attacks of mild to moderate severity due to *C. albicans*, and these attacks occur in healthy adult women without any predisposing factors (152). In contrast, approximately 10% of women suffer from complicated *Candida* vaginitis, in which attacks either are more severe, occur on a recurrent basis, or are due to non-*albicans Candida* species. Patients with complicated *Candida* vaginitis frequently have predisposing factors in the form of uncontrolled diabetes or other immunosuppressive conditions. Accordingly, vaginitis caused by *C. glabrata* represents a complicated form of disease.

Most clinical series have found that *C. albicans* is responsible for approximately 90% of episodes of *Candida* vaginitis. In the last decade, there have been increasing reports of vaginitis due to non-*albicans Candida* species. In these patients, *C. glabrata* is the most common organism isolated (18, 151). Whether there is a real, absolute increase in vaginitis episodes caused by *C. glabrata* or whether the reported incidents reflect an increased awareness resulting in more frequent cultures taken, as opposed to routine microscopy, is unclear. Unfortunately, epidemiological studies do not include sentinel screening sites, but depend on data obtained from tertiary-care centers, which reflect a major acquisition bias in the overall prevalence and distribution of *Candida* species. The apparent increase in vaginitis caused by non-*albicans Candida* species is thought to reflect the increased use of short courses of both topical and oral azole antimycotic regimens. Other theories include the widespread use and abuse of topical over-the-counter antifungal agents. Finally, some investigators have postulated that *C. glabrata* infections emerge as breakthrough vaginal infections in women receiving long-term maintenance low-dose fluconazole prophylactic regimens. In prospective longitudinal studies performed by Fidel and coworkers, the emergence of non-*albicans Candida* species causing breakthrough *Candida* vaginitis in women already receiving maintenance azole therapy was not apparent in studies performed over many years (97). In contrast, HIV-positive women treated with fluconazole (200 mg) once weekly as long-term suppressive maintenance chemoprophylaxis showed a moderate shift in vaginal mycoflora while demonstrating effective reduction in episodes of *Candida* vaginitis (141). The vaginal flora in women receiving fluconazole shifted to an increase in absolute isolation rates of *C. glabrata*, but with a low attack rate of clinical vaginitis.

Although it was postulated that HIV infection would be associated with an increased prevalence of vaginal non-*albicans Candida* species in a manner similar to the emergence of OPC caused by non-*albicans Candida* species, no such data have emerged to date in HIV seropositive women. In a women's cohort study (142) (HIV Epidemiological Research Study [HERS]), both baseline and follow-up studies failed to identify an increased colonization rate as well as vaginitis caused by non-*albicans Candida* species in HIV-positive women. Similarly, in contrast to OPC, non-*albicans Candida* species as well as *C. albicans* did not emerge with increased frequency in women with low CD4 counts (142).

In small clinical studies, a variety of risk factors have emerged for *C. glabrata* vaginitis. These include older patients, underlying medical conditions such as uncontrolled diabetes mellitus, and douching (53). Given the small number of patients with *C. glabrata* vaginitis, no large-scale studies have described the clinical characteristics of vaginitis caused by *C. glabrata*. It is widely assumed that clinical symptoms would be identical. Geiger et al., however, have reported subtle differences in the clinical presentation of *C. glabrata* vaginitis (53). In a study of 80 patients, an abnormal discharge was less frequently reported in women with symptomatic vaginitis due to *C. glabrata* in comparison to *C. albicans*. This may reflect the effects of lack of hypha formation by the *C. glabrata* blastoconidia. In general, vaginitis due to *C. glabrata* was reported to be more indolent with reduced inflammation and hence less dyspareunia. In addition, patients with *C. glabrata* vaginitis frequently reported a burning sensation as an alternative to itch. Clinical findings of the inflammatory reaction in the vulva and vestibule were similar to those associated with *C. albicans*. In contrast, speculum examination of the vagina, although revealing diffuse erythema, rarely revealed a caseous discharge in the presence of *C. glabrata*.

Diagnosis of *C. glabrata* vaginitis is more difficult than that of typical *Candida* vaginitis. This is because of the failure of the *C. glabrata* organisms to form pseudohyphae and hyphae 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.

(ii) Management. There is scant information on guidelines for management of vaginitis due to *C. glabrata*. In virtually all clinical studies of yeast vaginitis, patients with vaginitis due to *C. glabrata* were excluded or the numbers were not large enough that any variable response rate was detectable, even in large studies. Accordingly, the clinical response of patients with *C. glabrata* vaginitis to conventional topical or oral therapy is largely unknown. Published experience in the management of *C. glabrata* patients reflects a biased view of patients referred to specialized clinics only after they have failed to

respond to a large number of topical and oral azole agents (53, 151, 159). The percentage of patients with *C. glabrata* vaginitis, seen by primary care practitioners, who respond to initial courses of azole therapy is therefore unknown.

In vitro studies reveal that the MICs of all available azoles for *C. glabrata* are higher than that for most *C. albicans* isolates (96). The increase in MICs varies, however, with the specific azole. Butoconazole shows excellent in vitro activity, as do miconazole and clotrimazole. Terconazole, itraconazole, and ketoconazole show moderate activity. Fluconazole shows relatively poor in vitro activity, and, not infrequently, there is frank resistance. Published studies, of which there are few, reveal that in spite of in vitro activity, azole therapy does not predictably eradicate *C. glabrata* in vivo (125, 151). If an attempt is to be made to treat *C. glabrata* with either oral or topical azole therapy, fluconazole should not be the drug of choice, and all the other azoles agents should not be prescribed as short course regimens, i.e., single-dose or 1- to 3-day regimens. Accordingly, in a previously untreated patient, it is not unreasonable to use nonfluconazole azoles for 7 to 14 days.

Sobel et al. recently reported on the successful use of boric acid vaginal capsules in the treatment of *C. glabrata* vaginitis in women who had failed several courses of azole therapy (151). Boric acid, 600 mg in gelatin capsules, was administered intravaginally once a day for 14 days. In uncontrolled studies, the success rate measured by mycological eradication of the organism approximated 70%. Approximately 30% of the patients remained culture positive, and many of these returned within a short period with recurrence of vulvovaginal symptoms. These patients were then retreated with boric acid and given a maintenance regimen of boric acid prescribed several times a week for an additional period. However, the safety of the latter regimen is unknown, and, given the potential systemic toxicity of boric acid, it should not be undertaken lightly. As an alternative to boric acid maintenance therapy, nystatin vaginal suppositories (100,000 U daily) can be used as a maintenance regimen following the initial clinical and mycological successful therapy with boric acid. For patients who fail to respond to boric acid or for whom the boric acid or nystatin maintenance therapy becomes ineffective, topical flucytosine prescribed once a day for 14 days is generally recommended. A maintenance regimen with flucytosine is not available because of local toxicity, expense, and the potential for development of resistance. Most patients who receive flucytosine do extremely well, since *C. glabrata* is highly sensitive to this drug. For patients who fail to respond to both boric acid and flucytosine regimens, combination regimens including a topical antifungal such as boric acid, flucytosine, and nystatin can be coadministered with oral itraconazole. Although the value of oral itraconazole as definitive therapy is largely unknown, itraconazole demonstrates considerable in vitro activity (96). Based on disk agar diffusion susceptibility testing, terconazole has been considered to be highly active against *C. glabrata*; however, clinical experience with terconazole does not indicate any advantage over any of the other topical agents (151).

To date, it is unclear whether recurrent vaginitis due to *C. glabrata* is due to the same pathogenic mechanisms as recurrent vaginitis due to *C. albicans*. With *C. albicans*, a host factor rather than the lack of susceptibility of a microorganism to therapy is postulated to be responsible for recurrent disease (40, 149). In contrast, the additional element contributing to recurrence of *C. glabrata* infection is likely to be the resistance of the organisms to antifungal agents rather than a host factor. Nevertheless, in some patients, both components may be active. The treatment of *C. glabrata* vaginitis in HIV-positive women follows the same principles, and there is no evidence of higher failure rates.

Urinary tract. (i) Clinical manifestations. Urinary tract infections due to *Candida* species have markedly increased in the last two decades (132). *Candida* species are now responsible for approximately 10% of urinary tract infections in hospitalized patients (185). In contrast to OPC and vaginal candidiasis, approximately 50% of urinary isolates of *Candida* are due to non-*albicans Candida* species, the most common of which is *C. glabrata*. In a recent large multicenter study, *C. glabrata* was responsible for 20% of the *Candida* urinary tract infections (153). Not infrequently, *C. glabrata* is part of a polymicrobial infection, including either bacterial uropathogens or a second *Candida* species, usually *C. albicans*.

No unique epidemiological risk factors for *C. glabrata* urinary tract infections have been reported, although underlying diabetes mellitus is by no means an infrequently associated factor. Similar to *C. albicans* urinary tract infections, the majority of *C. glabrata* urinary tract infections occur in elderly hospitalized, debilitated, and catheterized patients who have recently received antibacterial agents.

The clinical spectrum of *C. glabrata* urinary tract infections appears identical to that caused by other species of *Candida*. The majority of patients are asymptomatic. Rarely do lower urinary tract symptoms develop, especially in catheterized patients. The risk of an ascending infection with involvement of the kidneys is rare and occurs mostly in patients with foreign bodies or stents and in the presence of obstruction. Rarely does *C. glabrata* fungemia complicate ascending *Candida* pyelonephritis. To complete the picture, candiduria caused by *C. glabrata* rarely complicates hematogenous candidiasis, in which renal candidiasis occurs with subsequent seeding of the urine. The diagnosis of *C. glabrata* urinary tract infection, although confirmed on culture, is usually suggested by the presence of budding yeast without hypha formation on microscopy of urine samples. The finding of *C. glabrata*, even in large numbers, in the urine, while indicative of urinary tract infection, does not localize the anatomical site of infection, which requires clinical correlation. Identifying the site of infection forms the basis for successful management.

(ii) Management. Asymptomatic candiduria is generally not treated. The natural history of asymptomatic candiduria is such that the candiduria often resolves spontaneously, especially when catheterization is changed or discontinued. Moreover, ascending infections resulting in sepsis are infrequent. Asymptomatic candiduria should be treated following renal transplantation, in neutropenic patients, and before attempting elective instrumentation or surgery of the urinary tract.

Symptomatic urinary tract infection caused by *C. glabrata*, although often successfully treated with amphotericin B blood irrigation or washout, may be effectively treated by systemic therapy with either amphotericin B or fluconazole. In a recent study of a large number of patients with asymptomatic candiduria, *C. glabrata* urinary tract infection appeared to respond to fluconazole therapy (200 mg/day) for 14 days at the same rate as did *C. albicans* infection. In a logistic regression analysis, *C. glabrata* species did not emerge as a factor influencing the outcome of antifungal therapy (2).

Systemic Infections

Advances in medical technology have had a major effect in reducing the morbidity and mortality of previously fatal diseases. With these benefits has come an increase in nosocomial fungal infections, primarily due to *Candida* species (3, 7, 31). Candidal infections may involve any anatomical structure and

are the cause of more fatalities than are any other systemic mycosis (115). A myriad of predisposing factors for systemic candidal infection have been previously identified (14, 90). Although few studies have evaluated specific risk factors for systemic *C. glabrata* infection, the risk factors leading to infection are similar to those from *C. albicans* infections. In one prospective epidemiological study evaluating *C. glabrata* colonization in medical intensive care units and in bone marrow transplant patients, the significant risk factors for nosocomial colonization with *C. glabrata* were prolonged hospitalization and prior antimicrobial use (170). A more recent concern, however, has been the numerous reports describing the increasing incidence of colonization and infection by non-*albicans Candida* species (specifically *C. glabrata* and *C. krusei*) in immunocompromised hosts (113, 180–182, 184). The increase in the infections by non-*albicans Candida* species is postulated to be associated with the increasing use of antifungal agents. According to several investigators, the increase in the frequency of *C. glabrata* infections has paralleled the increase use of fluconazole in some hospitals (1, 181–184). In a more recent study, however, investigators described the association between *C. glabrata* infection and amphotericin B use rather than fluconazole (112a). *C. glabrata* is of special importance because of its reduced susceptibility to antifungal agents (100, 129).

Clinical manifestations. *Candida* may involve any organ system, and candidemia has a diverse clinical picture, ranging from low-grade fever to fulminant septic shock. There are no characteristic signs and symptoms in disseminated candidiasis. Similarly, no unique clinical features are associated with *C. glabrata*. Often, the only manifestation is persistent fever in a patient whose condition is deteriorating and who is unresponsive to antimicrobial agents and has negative blood cultures. *C. glabrata* fungemia has been associated with a higher mortality rate than *C. albicans*. In fact, Komshian et al. reported a 100% mortality in 12 patients with *C. glabrata* fungemia (90). The higher mortality rate described by some investigators may not signify increased virulence but may reflect the more advanced state of debilitation in patients who acquire *C. glabrata* infection. In a more recent study, Fraser et al. found no difference in mortality rates between *C. albicans* and *C. glabrata* (51).

Management. Amphotericin B has been the "gold standard" in systemic fungal infections including candidemia, despite having a high adverse effect profile. Recently, prospective randomized clinical studies concluded that fluconazole, at a minimum dose of 400 mg/day, is as effective as amphotericin B in the management of candidemia in neutropenic and nonneutropenic patients. In addition, fluconazole is better tolerated and has fewer adverse effects (2, 130). Unfortunately, as in previous clinical antifungal trials, the majority of patients treated in these studies were infected with *C. albicans* and few had non-*albicans Candida* species, including *C. glabrata*. Accordingly, a *Candida* species-specific subanalysis and conclusion was not possible. Physicians are left to extrapolate the data obtained from the clinical trials treating *C. albicans* to managing infections due to *C. glabrata*. All antifungal agents have higher MICs for *C. glabrata* strains than for *C. albicans* (129). Thus, until more data are available, many clinicians treat *C. glabrata* fungemia with high-dose amphotericin B (0.6 to 1.0 mg/kg/day) or fluconazole (10 to 15 mg/kg/day) until the in vitro susceptibility data indicate that the clinical isolate is susceptible to fluconazole. After resolution of fungemia, the treatment course may be completed with oral fluconazole (30). Amphotericin B is more likely to be chosen to treat the hemodynamically unstable and septic patient.

In the past, many patients with life-threatening candidiasis died without receiving antifungal therapy. Clinicians are frequently required to act definitively and early on the basis of a high index of suspicion. To be effective, any therapy must be given early and, regrettably empirically, in the febrile high-risk patient. Empirical therapy with amphotericin B is especially indicated in the granulocytopenic patient with persistent fever after 3 to 7 days of antibiotic therapy, even in the absence of microbiological confirmation. Amphotericin B has been the drug of choice in this setting. This choice is especially justified since several investigators have documented the increase in the isolation of *C. glabrata* and *C. krusei* in neutropenic patients (181–184). There are no data on the role of the new lipid formulation of amphotericin B in treating *C. glabrata* fungemia. Although these new formulations result in higher-dose amphotericin B administration, superior success rates have not been determined.

ANTIFUNGAL RESISTANCE

Classification

Antifungal resistance can be divided into two categories: clinical resistance and in vitro resistance. Clinical resistance signifies a lack of a clinical response to the antifungal agent used. More often than not, clinical failure is due to low levels of the drug in serum and/or tissues for numerous reasons, most notably noncompliance with the medication regimen. Finally, one significant reason for clinical failure or resistance in AIDS patients is the presence of a severely immunosuppressive state, where the antifungal agents alone, including high-dose fungicidal agents, are unable to eradicate the fungi from the host.

In vitro resistance can be subdivided into primary resistance and secondary resistance. Primary resistance is also known as intrinsic or innate resistance and occurs when the organism is naturally resistant to the antifungal agent (e.g., *C. krusei*, which is known to be universally resistant to fluconazole) (183). On the other hand, secondary or acquired resistance is described when the isolate producing infection becomes resistant to the antifungal agent. This form of resistance, which was rare in the past, is now the most frequently reported form in AIDS patients who suffer from recurrent azole-resistant oropharyngeal or esophageal candidiasis (36, 49, 76, 83).

Evidence for Clinical and In Vitro Resistance

Antifungal resistance in *Candida* species was virtually nonexistent until the arrival of HIV infection. In the past, even when resistance was described, it was generally associated with the imidazole class of antifungal agents and was usually discovered in patients with chronic mucocutaneous candidiasis, who were being given chronic ketoconazole therapy (68). However, there are now numerous reports of oral thrush and esophageal candidiasis that are clinically refractory to all azole and polyene antifungal agents (28, 49, 78, 83, 98, 137). Under the selective pressure of numerous antifungal agents, populations of resistant or relatively resistant yeasts have emerged. There are numerous case reports describing the colonization and infection of compromised patients taking long-term oral antifungal agents, from whom *C. krusei* and *C. glabrata* with documented in vitro antifungal resistance have been recovered (181–184). Even amphotericin B-resistant *C. albicans*, *C. guilliermondii*, and *Cryptococcus neoformans*, a rare phenomenon in the past, have recently been reported (6, 173). These resistant yeasts are capable of producing debilitating and invasive fungal disease that is more difficult to eradicate (6, 78, 123). Overall, compared to other *Candida* species, especially *C. albicans*, *C. glabrata* isolates tend to be associated with higher

MICs of all azoles and are innately less susceptible to all antifungal agents including amphotericin B (170, 171). The frequency or prevalence of azole-resistant *C. glabrata* is unknown. Fluconazole-resistant isolates have been found predominantly in AIDS patients with OPC and esophageal candidiasis. In addition, resistant isolates have been found in fungemic patients and among vaginal isolates. In some cases, primary in vitro resistance to fluconazole has been reported (128, 129). By far, however, secondary in vitro resistance is the most common form of resistance in *C. glabrata* (181, 182, 184) and is most often seen for fluconazole. The reason for this rapid development of secondary antifungal resistance is unknown, but the haploid state of *C. glabrata* is thought to be a contributing factor. In contrast, in vitro resistance of *C. glabrata* and *C. albicans* to ketoconazole and itraconazole is somewhat less common (<15%) yet still significant. Several clinical studies have documented the selection of *C. glabrata* in patients treated with fluconazole for prolonged periods (128, 129), whereas *C. albicans* resistance to fluconazole had been rare. Accordingly, the use of intermittent versus continuous long-term azole therapy needs to be compared, as does the need to establish the minimum effective dose which will not select for resistant strains of *C. albicans* or the selection of more resistant *Candida* species, including *C. glabrata* (94).

An emerging dilemma is the development of multi-azole cross-resistance in *Candida* isolates recovered from AIDS patients with fluconazole-refractory OPC (112, 170). In one study, 45 isolates from 41 patients who failed to respond to at least 400 mg of fluconazole per day underwent in vitro testing. Twenty-seven *C. albicans* isolates had fluconazole MICs of >20 μg/ml; 41% of these isolates were also cross-resistant to clotrimazole, while another 11% were cross-resistant to itraconazole and ketoconazole (112). In another recent study, the authors evaluated 25 *C. glabrata* isolates recovered from patients with fluconazole-refractory OPC. Of these *C. glabrata* isolates, 68% were fluconazole resistant, and of these, 94% were also cross-resistant to ketoconazole and 88% were also cross-resistant to clotrimazole (170). In contrast, in the same study, 60 *C. albicans* isolates were recovered from similar patients, and while 78% were resistant to fluconazole, only 7% were cross-resistant to itraconazole, 11% were cross-resistant to ketoconazole, and 41% were cross-resistant to clotrimazole.

Fortunately, clinically significant amphotericin B resistance is still very uncommon among most *Candida* species except for *C. lusitaniae* and *C. guilliermondii*. Similarly, amphotericin B resistance has not been described in *C. glabrata* (52), although the MICs are higher than those seen for *C. albicans*.

Flucytosine resistance has been described extensively in *C. albicans*. Primary resistance rates vary from 5 to 50% depending on the species of *Candida* and the technique used to perform the susceptibility studies (54, 144, 173). Flucytosine resistance is also very common in *C. tropicalis*, *C. krusei*, and *C. parapsilosis*, many isolates of which have greater primary resistance rates than do *C. albicans* isolates (50, 118, 119, 144). In contrast, the majority of *C. glabrata* isolates are exquisitely susceptible to flucytosine. Flucytosine has not been widely used in *C. glabrata* infections but may be useful in the future.

Mechanisms of Resistance

The specific mechanisms of antifungal resistance to the azole class of antifungal agents are not yet fully understood. It has been suggested, however, that the sterol composition of the fungal plasma membrane is altered, thus reducing the uptake of the antifungal agent into the cell (146). Recent studies with several different azoles evaluating *C. albicans*, *C. glabrata*, and *S. cerevisiae* have demonstrated at least three known mechanisms of resistance: (i) changes in the P-450 lanosterol demethylase enzyme, (ii) changes in Δ^{5-6}-sterol desaturase, and, more recently, (iii) an energy-dependent drug efflux mechanism (63, 64, 116, 117). In *C. glabrata*, several mechanisms of azole resistance have been identified: increased P-450-dependent ergosterol synthesis and an energy-dependent efflux pump of fluconazole, possibly via a multidrug resistance-type transporter (117, 165, 166, 173).

Clinical Relevance

The clinical effects of antifungal resistance in the AIDS population were recently demonstrated by Koletar et al. (88). The authors evaluated AIDS patients who failed to respond to standard antifungal therapy for OPC and reported a median survival of 184 days after the onset of fluconazole-resistant thrush and only 83 days after the onset of clinical resistance to amphotericin B. Although mucosal candidiasis does not result in death directly, clinical antifungal failure is most probably a comorbidity factor in the rapid demise of these patients. The estimated frequency of azole resistance is still unknown; it is postulated that 4 to 6% of *C. albicans* isolates recovered from persons with AIDS are resistant to antifungal agents (27). In contrast, the frequency of resistance in *C. glabrata* is relatively unknown and difficult to predict, since few studies have addressed the issue. In those that have, few reports have described the incidence of azole resistance among any of the non-*albicans Candida* species, including *C. glabrata* (126, 127).

The management of fluconazole-resistant mucosal candidiasis is frequently unsatisfactory or short-lived, with periodic and rapid recurrences. Some patients will respond to a doubling of the dose of fluconazole. For example, if they fail to respond to 200 mg/day, an increase to 400 mg/day will frequently produce a clinical response for a while. However, the improvement is generally transient, and the infection recurs rapidly once this stage of the disease is reached. Several recent studies of the itraconazole oral solution have demonstrated promising results in AIDS patients who have not responded to fluconazole at 200 mg/day (22, 33, 121). These studies have demonstrated clinical cure and improvement in 55 to 70% of patients entered into the study. As expected, mycological cure rates were very low (<30%) and relapses were rapid (usually within 14 days) once the itraconazole solution was terminated. The recent approval of amphotericin B oral suspension is a new therapeutic option in these patients with azole-unresponsive mucosal candidiasis (113). In several small studies, the clinical improvement rates varied from 50 to 75%, but as with all these patients, the relapse rate is high and usually occurred within 4 weeks (113, 173).

Several new antifungal compounds are currently in various phases of development, and the results appear encouraging in early in vitro trials. Two new azoles, voriconazole and SCH 56592, have excellent in vitro activity against fluconazole-resistant *C. albicans* and *C. glabrata* isolates (91, 93, 136). In addition to the azoles, a new group of antifungal agents, the pneumocandins, are being evaluated in clinical trials. MK-911, a new parenteral pneumocandin, is currently in clinical trials in the United States. In vitro results with this new antifungal drug are very promising for many *Candida* species, including fluconazole-resistant *C. albicans*. In addition, the in vitro activity against *C. glabrata* and *C. krusei* is excellent (173).

CONCLUSION

Candida glabrata is emerging as a major pathogen in the 1990s. Previously largely ignored, this organism received little attention; therefore, not surprisingly, our knowledge of it is not only incomplete but also significantly lacking. We now have the molecular tools to study the epidemiology of *C. glabrata*, and investigations are needed. With *C. glabrata* increasingly being recognized as a problem pathogen in superficial and systemic candidiasis, host risk factors need additional study, as do important virulence factors. A major issue is the management of *C. glabrata* infections. Symptomatic infection is more difficult to eradicate with all of the available antifungal drugs. The azole antifungal agents that have proven so successful against *C. albicans* have been woefully inadequate against *C. glabrata* vaginitis, although these azoles appear adequate for *C. glabrata* fungemia. Understanding the mechanism of innate and acquired resistance may facilitate the development of new targets for novel antifungal agents. In any event, if *C. glabrata* infections are to be adequately controlled in the future, comprehensive studies of their epidemiology, pathogenesis, and resistance must be performed.

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