The Emergence of Non-*albicans* *Candida* Species as Causes of Invasive Candidiasis and Candidemia

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The last three decades have seen an expanding pool of high-risk patients susceptible to the opportunistic pathogen *Candida*. Accordingly, a dramatic increase in nosocomial blood stream infections (BSIs) due to *Candida* spp has been reported throughout the world, starting in tertiary care centers and spreading to community hospitals. This absolute increase in *Candida* BSIs was accompanied by both an absolute and then a proportional increase in invasive infection caused by reduced fluconazole-susceptible non-*albicans* *Candida* spp. Currently, the incidence trend of BSI has stabilized, and *Candida albicans* remains the most common species causing fungal BSI. Clinicians must be aware of the importance and implications of non-*albicans* *Candida* spp when selecting antifungal drugs, although most studies have not shown significant outcome differences with use of the various antifungal classes.

Introduction

Candida is among the leading causes of nosocomial blood stream infections (BSIs) worldwide [1,2•]. Risk factors for invasive candidiasis are well known, including *Candida* colonization, neutropenia, length of hospital stay, abdominal surgery, use of parenteral nutrition, broad-spectrum antibiotics, central venous lines, and hemodialysis [1,3,4]. Studies assessing nosocomial BSIs from 1980 to 1996 ranked *Candida* spp as the fourth most common nosocomial blood stream pathogens, representing approximately 8% of all healthcare-related BSIs in the United States [5]. During this time period, the incidence of *Candida* BSIs steadily rose due to higher numbers of susceptible patients and invasive procedures [5,6]. *Candida* remains an important cause of sepsis, especially in the intensive care unit, where sepsis due to fungal species increased 207% between 1979 and 2000 [7]. Crude mortality rates for candidemia ranged from 30% to 61% with significant attributable mortality 10% to 30% related to *Candida* [8,9].

In the last decade (1995-2005), a stable incidence trend of *Candida* BSI has become evident, although some reports, especially those dealing with specific populations (ie, intensive care units), now report decreasing trends [2•]. These units with the highest incidences of *Candida* BSI observed reduced candidemia due to better intravenous catheter utilization and use of antifungal prophylaxis [10,11]. A similar reduction in BSI due to *Candida* has been seen in patients with hematologic malignancies, especially those undergoing bone marrow transplantation [12]. Once more reduction in candidemia incidence is attributed to widespread routine use of fluconazole prophylaxis during periods of prolonged neutropenia together with shortened duration of neutropenia, less mucositis, improved catheter use, and earlier empirical antifungal drug initiation in febrile patients before candidiasis is confirmed.

Changing Epidemiology of Invasive Candidiasis

From 1970 to 2000, *Candida albicans* dominated as the causal *Candida* pathogen worldwide in BSIs and all forms of systemic candidiasis [13,14]. Significant changes in the last decade have transpired with a progressively important role of non-*albicans* *Candida* spp imparting a profound influence on selection of antifungal drugs (Fig. 1).

A shift to increased prevalence of non-*albicans* *Candida* spp has occurred, including patients who experience breakthrough infection with non-*albicans* *Candida* strains and resistant *C. albicans* [12]. However, considerable institutional variation remains, and not every site has reported a decrease in the proportion of infections caused by *C. albicans*. Approximately half the sites studied

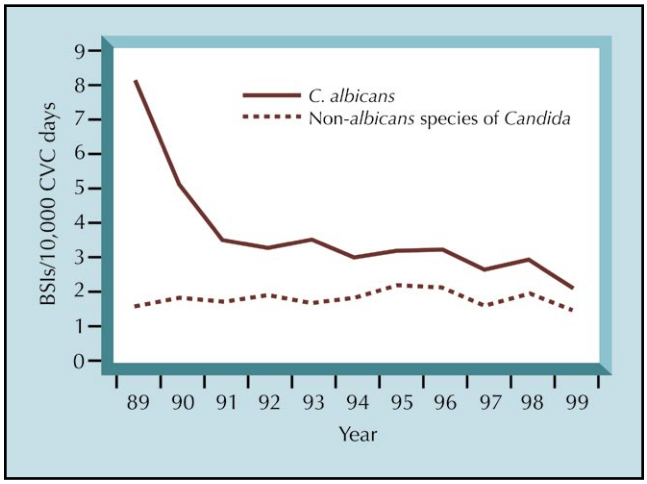

Figure 1. Incidence of hospital-acquired bloodstream infections (BSIs) due to *Candida albicans* and non-*albicans* species of *Candida* in National Nosocomial Infections Surveillance System intensive care units in the United States, 1989–1999. CVC—central venous catheter. (*From* Trick et al. [10], with permission.)

Table 1. Factors associated with the emergence of non-*albicans Candida* infections

Exposure to azoles including breakthrough infections
Severity of immunosuppression:
HSCT vs solid organ transplantation
Liver vs renal transplantation
Anatomical site:
Urinary tract vs oral mucosal candidiasis
Age:
Elderly have increased incidence of *Candida glabrata*
Neonates have increased risk of *Candida parapsilosis*
Geographic:
A decreased incidence of *C. glabrata* in Asia and Latin America

HSCT—hematopoietic stem cell transplant.

reported a reduction in the proportion of BSI caused by *C. albicans*, with *C. albicans* responsible for only 40% of *Candida* BSIs in isolated institutions [2•,15]. The majority of centers, especially those based in communities where azole prophylaxis is not used widely, showed a stable proportion of disease caused by *C. albicans* over time [2•]. In North America, the decrease in *C. albicans* was accompanied by a relative increase in *Candida glabrata* [10,16] followed by *Candida parapsilosis* [16,17].

Although anything but unequivocal, the switch to non-*albicans Candida* spp has been attributed to azole use, particularly fluconazole, both as prophylaxis and treatment of fungal infections in patients at high risk of *Candida* BSIs [3,18,19]. This issue remains controversial.

Also, underlying host factors contribute to the emergence of non-*albicans Candida* spp. For example, patients with solid tumors are at lower risk, whereas patients with hematologic malignancies or undergoing liver transplantation have a significantly high proportion of non-*albicans Candida* infection (Table 1). These underlying host factors together with previous antifungal therapy affect colonization patterns allowing increased presence in meaningful numbers of non-*albicans Candida* spp.

In perhaps the largest study of candidemia isolates, involving more than 6000 isolates obtained worldwide and collected over 10 years, Pfaller et al. [20•] reported that *C. albicans* remained the dominant *Candida* sp, averaging 55.9% and showing no tendency to decrease. *C. glabrata* isolates have increased in frequency. They average 16.2%, ahead of *C. parapsilosis* at 13.1% and *Candida tropicalis*, which at 9.6%, have significantly decreased in frequency. *Candida krusei* remained uncommon at 2.5%.

In different geographic areas, significant variation in the distribution frequency of *Candida* spp have been reported [21]. The frequency of *C. albicans* as a cause of BSIs ranged from 46.6% in Latin America to 73.5% in the Asia-Pacific regions. *C. glabrata* was the least common cause of BSIs in Latin America (7.5%) but the most common non-*albicans* species to cause BSIs in Canada (20.1%) and the United States (18.3%), with an increased frequency in North America over the decade studied [22].

In the United States, *C. albicans* was the predominant species in all regions studied; however, in three regions—Pacific, East North Central, and New England—its incidence dropped to below 50% [21,23]. *C. glabrata* was the second most common species, except in the West South Central region, where it was superseded by *C. parapsilosis* [21]. The final analysis found considerable differences in the distribution frequency of *Candida* spp between institutions, regions, and countries.

Differences Among *Candida* Species

The explanation for the variable distribution frequency of *Candida* spp within and between different institutions is largely unknown (Table 1). *C. albicans* has always been the dominant (almost universal) species colonizing all mucosal surfaces. This dominance is attributed to its enhanced capacity to adhere to epithelial cells in vitro. Several additional factors may contribute to the changing epidemiology of *Candida*. Of interest, all four predominant *Candida* spp have been shown to produce biofilms in vitro [24]. *C. parapsilosis*, in particular, colonizes normal skin leading to nosocomial spread by hand carriage and to persistence on inert surfaces in the hospital environment [25]. In contrast, *C. glabrata* is rarely cultured from skin and hands or the hospital environment, but only isolated from oral, gastrointestinal, and vaginal epithelial surfaces. Whenever *C. albicans* colonization of a mucosal surface changes and is eliminated under the influence of azole pressure, *C. glabrata* emerges as the most likely replacement

Table 2. Major pathogenic *Candida* species and their characteristics

Species	Characteristics
Candida albicans	Most common colonizing species
	Most common cause of mucocal and invasive disease
	Fluconazole resistance remains rare
	Echinocandin resistance extremely rare but recently reported
Candida tropicalis	Considered highly virulent
	Common in patients with hematologic malignancy
	Resistance is rare
Candida parapsilosis	Most common in neonates and children
	Less virulent, lower mortality
	Common skin colonization
	Usually related to intravenous catheter
Candida glabrata	Gastrointesinal colonization, azole pressure selection
	Important urinary tract pathogen
	More common in elderly, diabetics
	Higher incidence in North America
	Significant resistance to fluconazole
	Cross-resistance to other azoles
	Susceptible to flucytosine, echinocandin
Candida krusei	Uncommon cause of candidemia (< 3%)
	Intrinsic resistance to fluconazole
	Susceptible to voriconazole, posasconazole, and echinocandins

species. Understandably, local institutional antifungal pressure affects local epidemiology of candidemia, as it does antimicrobial resistance.

Non-*albicans Candida* spp are particularly prevalent in ascending urinary tract infections, whereas *C. glabrata* fungemia, which is uncommon in neonates, is most often seen in older adults [16] and those with chronic diseases (eg, renal failure and cerebrovascular accident) [26]. *C. tropicalis* tends to be associated with acute leukemia, bone marrow transplantation, and severe neutropenia. *C. krusei* is associated with prior fluconazole treatment (Table 2).

Selection of Non-*albicans Candida* Species

A widespread belief exists that exposure to antifungals, usually the azole class and particularly fluconazole, selects for non-*albicans Candida* spp by virtue of the exquisite susceptibility of *C. albicans* to triazoles [27]. This is certainly the experience in immunocompromised AIDS patients exposed repeatedly to fluconazole for recurrent oropharyngeal and esophageal candidiasis. In leukemic subjects in the 1980s, exposure to oral ketoconazole was predictably associated with initial disappearance of *C. albicans* from the gastrointestinal tract only to be followed by the appearance of *C. glabrata* in the feces. Similarly, in a prospective longitudinal study, HIV-positive women exposed to frequent courses of oral fluconazole demonstrated a vaginal appearance of *C. glabrata* [28]. However, not all studies have concluded that fluconazole exposure is responsible for the shift to non-*albicans* species [29]. Of interest is a case control study in which Lin et al. [29] concluded that rather than exposure to fluconazole, exposure to antibacterial agents, specifically vancomycin or piperacillin-tazobactam, was associated with subsequent nosocomial *C. glabrata* or *C. krusei* candidemia. The precise pathophysiologic role of antecedent antimicrobial agents in this context is unknown. Antibiotics enhance gastrointestinal carriage of yeast but why non-*albicans* species? *C. albicans* may respond to different antibiotic-selection influences.

Antifungal Drug Susceptibility Differences Among *Candida* Species

Within particular institutions, prior or concurrent antifungal drug pressure may affect not only the local epidemiology of candidemia but also antifungal resistance status, although the data are by no means conclusive.

Table 3. General patterns of susceptibility of *Candida* species

Candida species	Flu	Itr	Vor	5FC	AmB	Candins
Candida albicans	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S (to I?)
Candida glabrata	SDD to R	SDD to R	S to I	S	S to I	S
Candida krusei	R	SDD to R	S to I	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S to R	S

5FC—flucytosine; AmB—amphotericin B; candins—echinocandins; flu—fluconazole; I—intermediate; itr—itraconazole; R—resistant; SDD—sensitive dose dependent; vor—voriconazole.

In vitro susceptibility testing has been performed by several investigators on blood stream *Candida* isolates (Table 3) [13,20•,21,23,30–32,33•]. Consistently, *C. albicans*, *C. tropicalis*, and *C. parapsilosis* have been found to be extremely susceptible to available systemic antifungal agents [3,33•]. Azole resistance remains rare in these species. Although *C. parapsilosis* shows higher minimal inhibitory concentrations (MICs) against the entire echinocandin class compared to other *Candida* spp, values are well within the susceptible range (< 1 μg/ml). *C. krusei* is intrinsically resistant to fluconazole and frequently demonstrates reduced susceptibility to amphotericin B and flucytosine, although it is susceptible to caspofungin, voriconazole, and posaconazole [32].

However, *C. glabrata* is the problem species: though incident isolates are generally susceptible to fluconazole, about 10% of them are fluconazole resistant. Resistance is not intrinsic, as with *C. krusei*, but it develops rapidly, particularly in patients who have received prior fluconazole prophylaxis or treatment [10,30].

Though susceptible to triazoles, *Candida lusitaniae* is frequently resistant to amphotericin B and nystatin, related to the amount of ergosterol in the plasma membrane [30]. *Candida rugosa* has been reported to express decreased susceptibility to nystatin, amphotericin B, and fluconazole [30]. *Candida guilliermondii*, though uncommon, may occasionally be resistant to amphotericin B.

Geographic differences in the prevalence of *Candida* spp are also reflected in the frequency of drug resistance. Pfaller et al. [30] reported that in vitro susceptibility of *C. glabrata* BSI isolates to fluconazole was highest in the Asian/Pacific rim region (76% were fluconazole susceptible, 2% were fluconazole resistant) and lowest in the United States (58% were susceptible, 9% were resistant). Within the United States, marked variations were present among hospitals, with reported resistance rates ranging from zero to 23% [20•,30,34]. In the Pfaller et al. [30] study, all azole resistant isolates of *C. glabrata* were susceptible to caspofungin (MIC < 1 μg/ml). Cross-resistance to voriconazole and posaconazole occurred in about half the fluconazole-resistant strains [30]. Moreover, acquired stable resistance to fluconazole with cross-resistance to itraconazole and voriconazole may develop rapidly after extremely short exposure to fluconazole [35]. Acquired resistance to amphotericin B and caspofungin has also been reported in a critically ill transplant recipient [36].

Clinical Manifestations of Invasive Candidiasis Due to Non-*albicans Candida* Species Infection

Although several *Candida* spp, notably *C. glabrata* and *C. parapsilosis*, have shown reduced virulence in animal models, the clinical syndrome associated with invasive candidiasis due to non-*albicans* species in individual patients is indistinguishable from that caused by *C. albicans*, ranging from fever only in hemodynamically stable hosts to frank sepsis and fatal septic shock. *C. parapsilosis* is a common skin colonizer but an infrequent gut colonizer. Because neutropenic patients who develop candidemia do so most commonly from a gastrointestinal source, *C. parapsilosis* is an uncommon cause of candidemia in this population and usually indicates a vascular catheter source when found in blood culture.

Mortality of Non-*albicans Candida* Infections

Although some centers report an increased mortality associated with non-*albicans Candida* spp compared to *C. albicans*, no consistent pattern has emerged. Other multicenter studies show higher fatality rates with *C. albicans* [26]. In one study, despite the marked increase in proportion of candidemia episodes in a bone marrow transplant center due to non-*albicans Candida* spp, mortality from candidemia decreased substantially [12].

In addition to the virulence of the yeast strain involved, multiple host factors and treatment variables influence mortality. Accordingly, it becomes extremely difficult to compare species-attributable mortality. In general, crude mortality for candidemia varies from 20% to 61% (40% in adults, 22% in children) [1]. Attributable mortality ranges from 10% to 30% [1,37]. *C. parapsilosis* is consistently associated with a lower mortality [1]. Several investigators, though not all, reported higher mortality with *C. tropicalis* attributed to its greater in vitro virulence. Mortality rates for *C. glabrata* varied widely, but several reports indicate

a higher mortality, attributed primarily to the fact that *C. glabrata* infection tends to occur in sicker, older, more debilitated patients [16,26].

Breakthrough Non-*albicans Candida* Infections

Case reports of breakthrough BSIs caused by fluconazole-reduced susceptibility non-*albicans Candida* spp have been published. However, this is uncommon even in neutropenic patients, hence the continued widespread use of fluconazole prophylaxis in high-risk patients. Notably, breakthrough *C. glabrata* and Zygomycetes have been reported in non-neutropenic patients most commonly after hematopoietic stem cell transplant [38]. Clinicians must be aware of the risk of *C. glabrata* resistant to voriconazole causing candidemia.

Therapeutic Implications of Non-*albicans Candida* Species

The shift toward non-*albicans Candida* spp has profoundly influenced antifungal drug selection in clinical practice. In treating candidemia, clinicians select and implement antifungal therapy 24 hours or more before species identification is available and several days before antifungal susceptibility data are provided. Most practitioners do not have rapid access to in vitro susceptibility tests. Accordingly, at the time of drug selection the clinician only has the result of a blood culture identifying a yeast and frequently indicating *Candida*.

Knowing that a 20% to 50% chance exists in a given institution that the isolate is *C. glabrata* greatly influences initial empiric antifungal drug selection. *C. glabrata* is more likely the offending blood isolate in: 1) medical centers with a high prevalence of *C. glabrata*; 2) patients currently or recently exposed to azoles; and 3) patients with any culture data present in their charts of *C. glabrata* colonization of sputum, wound, or urinary catheters. In the final analysis, fear of *C. glabrata* and other less common fluconazole-resistant species (eg, *C. krusei*) is the driving force for clinicians to initiate therapy with a broad-spectrum antifungal agent echinocandin (eg, caspofungin, micafungin, anidulafungin) or voriconazole.

Within a few days, once the *Candida* sp is identified, this approach allows for a change to less expensive and narrower spectrum regimens (eg, fluconazole). Species identification has been found to be adequate in directing therapy because of the overall correlation between species identity and in vitro susceptibility [39••]. Routine susceptibility testing is not recommended, due to cost and the inevitable delay before results are available. Testing is indicated for persistent and recurrent candidemia, and for unique clinical scenarios (eg, *Candida* endocarditis), especially in the presence of non-*albicans Candida* spp.

In spite of in vitro verified differences in azole and echinocandin susceptibility among *Candida* spp, predictable species-specific clinical correlation in BSIs based upon in vitro susceptibility has not been forthcoming. Accordingly, in multiple large, prospective, multicenter studies designed to compare antifungal drug regimens, substudies comparing eradication and mortality rates among the various *Candida* spp have disappointingly failed to show clinical differences (ie, cure rates) among species, regardless of the antifungal drugs studied. One might have expected significantly lower cure rates in patients with *C. glabrata* BSI treated with fluconazole than in those with *C. albicans* or those with *C. glabrata* treated with amphotericin B. The explanation for this incongruity still eludes researchers for many reasons, including the limited number of patients with non-*albicans Candida* spp isolates, and most importantly, the enormous impact of host factors (eg, inconsistent catheter removal, abscess drainage) diluting the differences in organism drug susceptibility in trials. In a single retrospective study, however, Bodey et al. [40] observed that fluconazole was less effective against *C. glabrata* than against *C. albicans*, 20/38 (53%) versus 57/74 (77%) ($P = 0.008$).

One must focus on individual patients with antifungal drug failure to recognize outcome differences (eg, higher proportion of *C. parapsilosis* among patients failing caspofungin therapy) [9]. However, even this observation was not evident in a recent anidulafungin study [41•]. Experimental animal models that adequately control for host factors offer the best opportunity to verify the importance of in vitro sensitivity in determining drug selection. Individual cases are reported in which the reduced susceptibility or resistance of individual isolates, especially those of non-*albicans Candida* spp, do influence clinical outcome and validate the importance of in vitro susceptibility tests. Nevertheless, clinician awareness that non-*albicans Candida* spp are often less sensitive to azoles but not to echinocandins continues to drive management of fungal BSIs.

From a practical point of view, guidelines recommend against flucytosine and fluconazole to treat *C. krusei*, and they advise higher daily doses of amphotericin B (0.8–1.0 mg/kg) [39••]. Guidelines for *C. glabrata* are more controversial. In spite of the absence of good clinical data, some advocate the use of higher doses of fluconazole (12 mg/kg) aimed at those isolates with sensitive–dose-dependent (SDD) status. Most experts now recommend starting therapy with an echinocandin and possibly switching to fluconazole if the organism is susceptible to it. Reports show a growing number of refractory *C. glabrata* infections that fail azoles but respond to caspofungin. Clinicians should recognize the correlation between *C. glabrata* fluconazole susceptibility and susceptibility to voriconazole and posaconazole: half the fluconazole-resistant isolates are also resistant to the latest generation

triazoles. Accordingly, use of these newer agents for infections due to *C. glabrata* with fluconazole MICs greater than 8 μg/ml should be avoided. Similarly, caution is advised when considering voriconazole therapy for *C. glabrata* candidemia in patients with extensive prior azole drug exposure [42]. On the other hand, several in vitro and experimental animal studies concluded that voriconazole activity against *C. glabrata* can be enhanced by combination with amphotericin B and other agents (eg, terbinafine) directed against different yeast cell targets [43]. Similar complete eradication of *C. glabrata* was achieved in immunosuppressed mice by combination therapy of liposomal amphotericin B and caspofungin [44]. Although clinical experience is limited, refractory resistant non-*albicans Candida* infection may merit antifungal drug combination therapy.

Conclusions

A changing epidemiology of invasive candidiasis and candidemia is evident. Although *C. albicans*, specifically fluconazole-susceptible *C. albicans*, remains the most common fungal pathogen, non-*albicans Candida* spp, including *C. glabrata* and *C. parapsilosis,* have been increasingly isolated, leading to a profound effect on antifungal drug selection and strategies [45]. Of major concern is the increased prevalence of species resistant to fluconazole and occasionally even the newest triazoles (ie, voriconazole and posaconazole). In particular, acquired azole resistance, including azole class cross-resistance in *C. glabrata* impacts therapeutic drug use [46]. Echinocandins offer a reassuring spectrum activity against non-*albicans Candida* spp; however, the jury is still out with regard to *C. parapsilosis*, and acquired resistance to this class is minimal so far.

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