The Changing Face of Fungal Infections in Health Care Settings

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As strategies to prevent invasive fungal infections among both hospitalized and nonhospitalized patients have evolved, the epidemiology of these infections has changed. Several unique features of select Candida species and molds have facilitated the emergence of these pathogens as more-common causes of infection than in previous years. In this context, the changing pathogen profiles, unique antifungal susceptibilities, and approaches to treatment are outlined.

Since the early 1990s, patients have been offered more-advanced treatments for severe illness, malignancy, and hematological conditions in a wider variety of settings than in the past. These developments have resulted in a change in the epidemiology of health care–related fungal infections. This review highlights some of these changes, focusing on Candida bloodstream infections (BSIs) and the more common invasive mold infections, and it discusses some of the implications for the practicing clinician.

CANDIDA BSIs

Impact. Candida BSIs are frequently associated with a sepsis syndrome and often involve disease outside of the bloodstream [1, 2]. In fact, a subset of cases of candidemia may actually represent infection at ≥2 nonadjacent organs and constitute disseminated disease or invasive candidiasis [3, 4]. In these scenarios, disease may have spread from the gastrointestinal tract to catheters or other organs or have spread from catheters to other organs. This component of disseminated candidiasis may help explain why candidemia appears to be such a devastating disease. The attributable mortality for candidemia was assessed at a single medical center, where uninfected control subjects were matched by age, sex, underlying disease, time at risk, surgery, and clinical parameters. The attributable mortality rate was 49%, which was similar to that observed >1 decade earlier, despite the availability of several newer agents to treat this disease [5]. Data from a population-based case-control study from Baltimore and Connecticut were used to calculate an attributable mortality rate of 19%–24%, depending on the patients’ ages. When extrapolated to the United States, the estimated annual number of excess deaths due to candidemia was 4256–5376, and the estimated excess hospital costs were $44–$320 million [6].

Incidence and risk factors. Candida species are the most common cause of invasive fungal infections in hospitalized patients and the fourth most common cause of hospital-acquired BSI among intensive care unit (ICU) patients in the United States [4, 7]. The incidence of candidemia has been evaluated in several ways. Although recent estimates of incidence in a US study (8 cases per 10,000 discharges) [8] and in comparable European studies (2–5 cases per 10,000 discharges) [9–11] vary slightly, these data do not reflect changes over time. Interpretation of data that evaluate the incidence over time is challenging; here, we find conflicting results with regard to the state of candidemia over the past decade. In one Swiss study, the incidence remained stable among all hospitalized patients [10], whereas detailed data from a US study limited to ICU patients demonstrated a 30% decrease in incidence [12]. However, data from the US National Center for Health Statistics suggest that the number of patients discharged with sepsis caused by fungi has tripled over the past decade, with candidemia being the most likely cause of fungal sepsis in hospitalized patients [13].

One likely explanation for these apparently disparate findings is that advances in medical therapy have increased the number of patients susceptible to Candida BSI: patients are surviving...
longer as a result of advances in the management of critical illness, broad-spectrum antimicrobials are used more frequently, and life-saving therapies are being applied outside of ICUs. The established risk factors for candidemia, including prior colonization, use of central venous catheters and broad-spectrum antimicrobials, mucosal surface disruption (e.g., presence of cytotoxins, hypotension, and surgery), and neutropenia [4] are not limited to ICU patients anymore. In fact, a US population-based study found that one-third of patients with candidemia had disease onset in the hospital but outside of the ICU, whereas another one-fourth had disease onset outside of the hospital [8].

**Differences among Candida species.** Most BSIs due to Candida species are caused by either *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, or *Candida parapsilosis* [4, 8, 14]. The remaining infections tend to be caused by *Candida krusei, Candida lusitaniae, Candida guillermondii*, or *Candida rugosa*. Several of these species have unique properties that may interact with local factors and influence the epidemiology of candidemia in particular institutions (table 1). For instance, all 4 Candida species that are major causes of candidiasis have been shown to produce biofilms (microbial communities enclosed in a polysaccharide-rich matrix) in vitro [15]. Given the reduced ability of antifungal drugs to penetrate biofilms and to eradicate the organisms within, biofilm formation has been implicated as a contributing cause of primary BSIs associated with indwelling catheters and total parenteral nutrition administration. In addition to its ability to form biofilms, *C. parapsilosis* in particular also can colonize skin, leading to nosocomial spread by hand carriage and to persistence in the hospital environment [16, 17]. These factors all contribute to its prominence as a major cause of infection in neonates [8, 18].

Within particular environments, concurrent or prior antimicrobial pressure may also affect the local epidemiology of candidemia. Although this effect has been well documented for emerging antibacterial resistance [19], the data are less clear for antifungal resistance. Although there are standard methods published by the Clinical Laboratory Standards Institute (formerly NCCLS standard M27A2 from 2002) for in vitro antifungal susceptibility testing of *Candida* species, interpretative breakpoints exist only for fluconazole, itraconazole, voriconazole and flucytosine [20]. Limitations of testing include variability in interpretation of results (e.g., misinterpretation of trailing growth at high drug concentrations) [21] and the lack of a strong correlation between MIC data and clinical outcome for invasive disease (e.g., fluconazole breakpoints were based predominantly on mucosal candidiasis data) [20].

On the basis of several series in which in vitro susceptibility testing was performed on bloodstream isolates, *C. albicans*, *C. tropicalis*, and *C. parapsilosis* have been found to be very susceptible to existing systemic antifungal agents (table 1) [8, 22]. Alterations in the amount of ergosterol in the plasma membrane of *C. lusitaniae* can result in resistance to polyene agents (amphotericin B and nystatin) in some strains of this species, although they remain susceptible to triazoles (fluconazole, itraconazole, voriconazole, posaconazole, and ravuconazole) [20]. *C. krusei* is intrinsically resistant to fluconazole and often demonstrates decreased susceptibility to amphotericin B and flucytosine, although it remains susceptible to caspofungin, voriconazole, posaconazole, and ravuconazole [23]. *C. rugosa* has demonstrated decreased susceptibility to amphotericin B, nystatin, and fluconazole [23]. This property and a propensity to colonize skin may help explain how this species has caused several difficult-to-control outbreaks of infection in hospitals.

<table>
<thead>
<tr>
<th>Candida species</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Echinocandins</th>
<th>Flucytosine</th>
<th>Amphoterica B</th>
<th>Feature</th>
<th>Relative frequency, % of Candida BSIs</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>Causes BSI and deep organ infection</td>
<td>40–60</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>Causes BSI and myositis</td>
<td>15–25</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>Causes BSI; associated with use of devices; affects neonates</td>
<td>20–30</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>S-DD to R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to I</td>
<td>Causes BSI and UTI</td>
<td>15–25</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>I to R</td>
<td>S to I</td>
<td>Causes BSI; associated with transplantation</td>
<td>&lt;5</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
<td>Causes BSI and deep organ infection</td>
<td>&lt;5</td>
</tr>
</tbody>
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**NOTE.** Currently, the Clinical Laboratory Standards Institute (formerly the NCCLS) has established interpretive MIC breakpoints for Candida species isolates tested against fluconazole, itraconazole, voriconazole, and flucytosine using Clinical Laboratory Standards Institute-recommended guidelines for broth dilution testing. On the basis of these breakpoints, resistance is defined as an MIC of >64 µg/mL for fluconazole, >1 µg/mL for itraconazole and voriconazole, and >32 µg/mL for flucytosine [20]. Interpretive MIC breakpoints for other fungal pathogen-antifungal drug combinations covered in the Clinical Laboratory Standards Institute documents have not been defined. For purposes of this table, susceptibility is defined as an MIC of ≤1 µg/mL for amphotericin B and caspofungin, as in [23]. Data adapted from [4, 8, 14]. I, intermediate; R, resistant; S, susceptible; S-DD, susceptible, dose dependent; UTI, urinary tract infection.
However, C. glabrata has emerged as the problem Candida species of the decade; it is a very common cause of candidemia, usually ranking second or third after C. albicans. Although incident isolates are generally susceptible to fluconazole, this species can easily develop acquired resistance, particularly in patients who have received prior fluconazole prophylaxis or treatment [12, 14].

**Changing pathogen profiles.** Fluconazole became widely available in the early 1990s. Several reports have documented a shift in the species of Candida that cause candidemia when fluconazole is used as prophylaxis for the prevention of candidemia. Cancer centers using fluconazole prophylaxis reported higher numbers of C. krusei or C. glabrata infections during the 1990s, compared with historical figures at the same centers [26]. However, these numbers may not reflect the experience in patients without cancer who require shorter-term prophylaxis. A study involving >1000 ICUs at >300 US health care centers reported an increase in C. glabrata BSIs in their ICU patients over the past decade (from 0.2 to 0.6 C. glabrata BSIs per 10,000 central venous catheter-days) [12]. Despite this increase, however, the overall rate of candidemia (due to all species) is at its lowest (~3 cases per 10,000 central venous catheter-days) as a result of a decrease in the prevalence of C. albicans. In contrast, a large multicenter study of Swiss hospitals reported no shift towards C. glabrata or C. krusei, despite there being a 6-fold increase in the rate of fluconazole use at the study centers [10].

One factor that may influence the pathogen profile of candidemia may be differences in the properties of C. glabrata in different geographic areas. Pfaller et al. [27] described international differences in fluconazole susceptibility in vitro among C. glabrata strains that cause BSI. The susceptibility was highest in the Asian/Pacific Rim region (76% of isolates were fluconazole susceptible, and 2% were fluconazole resistant) and lowest in the United States (58% of isolates were susceptible, and 9% were resistant). Within the United States, there was also great variation between hospitals, with reported resistance rates ranging from 0% to 23%.

Prophylactic use of fluconazole is currently recommended in very specific patient populations (e.g., some bone marrow transplant or liver transplant recipients) who have a sufficient risk of invasive candidiasis to warrant prophylaxis [28]. In 2004, fluconazole became available as a generic agent. Since then, the use of fluconazole as either prophylaxis (i.e., it is administered to all patients admitted to a specific hospital ward) or preemptive therapy (i.e., it is administered to all patients at extreme risk for candidemia) is not uncommon in other populations. Clinicians considering empirical therapy for candidemia should take into account prior triazole exposure and the likelihood of infection with C. glabrata [28]. Currently, species identification or clinical parameters, not routine susceptibility testing, should guide initial therapy. When susceptibility testing is done, clinicians should recognize that there appears to be a correlation between susceptibilities to voriconazole, posaconazole, and ravuconazole and susceptibility to fluconazole [23], so use of these newer agents for infections due to C. glabrata with fluconazole MICs of ≥8 μg/mL should be avoided. However, C. glabrata appear to be consistently susceptible to caspofungin and fluconazole. Although echinocandin resistance among Candida species is extremely rare, one report describes the development of secondary multidrug (caspofungin-triazole) resistance in a patient receiving caspofungin and fluconazole for C. parapsilosis prosthetic valve endocarditis [29].

Infections or outbreaks of infection in hospitals can also be caused by non-Candida yeasts, some of which can be resistant to commonly used antifungals. Rhodotorula species, a common skin colonizer and contaminant of milk products, has emerged as a human pathogen in the context of central venous catheters and malignancies [23, 30]. Trichosporon asahii and Trichosporon mucoides can enter the bloodstream via catheters or the gastrointestinal tract and cause disseminated disease similar to hepatic candidiasis [31]. These yeasts should not be ignored when reported from hospitalized patients with central venous catheters, underlying malignancy, or neutropenia.

**INVASIVE MOLD INFECTIONS**

**Impact.** A study using the National Hospital Discharge Data from the 1990s estimated that 10,190 aspergillosis-related hospitalized admissions occurred annually in the United States, resulting in 1970 deaths and $633.1 million in costs [32]. Invasive aspergillosis is associated with extremely high mortality rates (~58%), despite the availability of highly active antifungal treatments [33]. The populations at greatest risk for these invasive Aspergillus infections are solid organ and hematopoietic stem cell transplant recipients. The incidence of disease varies greatly, however, even within this population. Nineteen US centers reported that the aggregate cumulative incidence of aspergillosis at 12 months after transplantation was 0.5% after autologous hematopoietic stem cell transplantation, 2.3% after allogeneic hematopoietic stem cell transplantation from an HLA-matched related donor, 3.2% after transplantation from an HLA-mismatched related donor, and 3.9% after transplantation from an unrelated donor (figure 1) [34]. Some of this variation is likely explained by differences in severity of graft-versus-host disease. However, many health care centers may be more inclined to treat suspected (i.e., probable) invasive mold infections without confirming the diagnosis by tissue biopsy, so multicenter studies of incidence are limited by intercenter variability in invasive diagnostic efforts.

The impact of more-novel transplant regimens, such as the use of peripheral blood stem cells, use of antithymocyte globulin, nonmyeloablative conditioning, or T cell-depleting ther-
Emerging Aspergillus infections. In a recent report from 19 US health care centers, isolates recovered during 72 cases of aspergillosis in hematopoietic stem cell transplant recipients included Aspergillus fumigatus (56% of cases), Aspergillus flavus (18.7%), Aspergillus terreus (16%), Aspergillus niger (8%), and Aspergillus versicolor (1.3%). Seven cases (10%) were due to multiple species [34]. This differs from data from the 1990s, when 90% of aspergillosis cases among hematopoietic stem cell transplant recipients in which isolates were recovered were reportedly due to A. fumigatus [33, 35, 37]. One center reported an increase in the percentage of aspergillosis cases caused by A. terreus from 2.1% of all cases in 1996 to 10.2% in 2001 [38]. The emergence of A. terreus may relate to several factors and is cause for concern. One factor may be improved means of recovery in the laboratory; A. terreus, unlike A. fumigatus, can be recovered in blood cultures much like other angioinvasive fungi, such as Fusarium, Scedosporium, and Acremonium species. Another more likely possibility may be alteration in the microbial flora of these patients from prior exposure to amphotericin B, to which A. terreus is resistant in vitro and in vivo [23]. It is likely that these factors—and, possibly, unmeasured environmental factors—will continue to play a role in the emergence of A. terreus in these high-risk populations.

The emergence of Zygomycetes. Overall, molds of the class Zygomycetes are a less frequent cause of infection than are Aspergillus species. Zygomycosis infection is lethal (mortality rate, ~80%), despite aggressive medical and surgical interventions. Voriconazole, an extended-spectrum triazole approved for the treatment of aspergillosis in May 2002, has poor activity against Zygomycetes. Recently, several health care centers have documented increases in zygomycosis since the availability of voriconazole [39–42]. According to these 4 studies, <1% of hematopoietic stem cell transplant recipients at these centers developed zygomycosis before the centers started using voriconazole for prophylaxis, and ~4% did after the introduction of voriconazole. Notably, this increase may not be entirely attributable to the introduction of voriconazole. It may be attributable to an unrelated temporal fluctuation in the environmental reservoir, or the patients’ underlying susceptibility to infection may be increasing over time.

On the other hand, prior to widespread availability of this agent, Marr et al. [35] reported that twice as many transplant recipients developed zygomycosis during the period of 1995–1999 than during 1985–1989. However, similar increases occurred for both aspergillosis and fusariosis as well, suggesting the increase may have more to do with patient susceptibility overall than with selective pressure for zygomycosis. The Transplant Associated Infection Surveillance Network reported preliminary data pooled from 16 transplant centers illustrating an increase since 2001 in the number of reports of zygomycosis, despite there being stable numbers of fusariosis and declining numbers of aspergillosis. However, these data still require proper adjustment (e.g., calculation of incidence by risk categories) to reflect true trends in incidence. The question remains: is any increase in the rate of zygomycosis a reflection of more patients surviving by avoiding an initial Aspergillus infection, or is it simply the result of alterations in the microbial flora in the patient? Either way, clinicians are likely to see more cases of zygomycosis in the coming years, particularly among transplant recipients and patients with cancer. Amphotericin B is the traditional agent of choice for these infections, because these species are often resistant to triazoles and echinocandins [23]. Some in vitro data suggest that posaconazole may be more active [23]. Combining pharmacologic therapy with surgical debridement often results in a more favorable response; how-

**Figure 1.** Cumulative incidence of invasive aspergillosis (IA) among autologous hematopoietic stem cell transplant recipients (solid line) and among allogeneic hematopoietic stem cell transplant recipients who received grafts from matched related donors (dashed line), mismatched related donors (dotted line), or unrelated donors (dashed line and dotted line). Reprinted with permission from [34].
ever, clinical trials and perhaps salvage therapy data are needed to better define the best approach to therapy.

**Other mold infections.** Three other mold infections should be noted. All of these molds appear to be resistant to amphotericin B and have caused breakthrough infections in high-risk patients exposed to amphotericin B. *Fusarium* species are found in the soil and can cause a range of infections in humans, from superficial or locally invasive skin infections to disseminated infections involving the bloodstream, sinuses, and lower respiratory tract. Although the environment outside of the hospital is thought to be the reservoir for most exposures, some evidence points to hospital-based exposure through contaminated water distribution systems [43]. In a recent study involving 9 transplant centers, fungemia and skin manifestations were reported in 44% and 75% of cases of fusariosis, respectively [44]. The most frequent species causing infections in humans include members of the *Fusarium solani* complex, *Fusarium oxysporum*, and *Fusarium moniliforme* [31, 35, 44]. Breakthrough infections have been reported during amphotericin B therapy, to which *Fusarium* species appear to be resistant in vitro; *Fusarium* species also appear to have in vitro resistance to the triazoles. The use of voriconazole as salvage therapy has been reported with some success, but immune reconstitution should be central to therapy, because persistent neutropenia is the main predictor of poor outcome [44]. Overall, the mortality rate usually exceeds 80% at 90 days after infection onset [35, 44].

*Scedosporium apiospermum* (teleomorph *Pseudallescheria boydii*) and *Scedosporium prolificans* are becoming more recognized causes of disseminated disease, often including pulmonary or CNS disease in patients with severe immunosuppression. The combination of a severely immunosuppressed host, a predilection for dissemination, and a lack of effective antifungal therapy results in almost universally fatal infections. Like *A. terreus* and *Fusarium* species, *Scedosporium* is capable of adventitious sporulation (sporulation in tissue), allowing for hematogenous spread and more frequent dissemination, compared with other *Aspergillus* species. A detailed review of infections among solid organ and hematopoietic stem cell transplant recipients at one medical center identified dissemination in >50% of *Scedosporium* infections [45]; fungemia was common and occurred in more than one-half of the *S. prolificans* infections. Likewise, a blood culture positive for these molds among patients with leukemia or hematopoietic stem cell transplant recipients should be considered clinically relevant. A review of 29 patients with cancer and blood cultures positive for molds found that 80% of blood cultures from which *S. prolificans* or *S. apiospermum* were recovered represented definite or probable fungemia, compared with 1 (4%) of 24 cultures in which other fungi (*Aureobasidium pullulans* and *Paecilomyces, Alternaria, Trichoderma, Bipolaris, or Chaetomium* species) were recovered [46].

Presently, it is difficult to know whether the recent appreciation of *Scedosporium* species as a pathogen is the result of better laboratory practices, or whether it is a result of a more susceptible population. However, several factors suggest the latter scenario may be more important. *Scedosporium* species are resistant to amphotericin B preparations. Moreover, *S. prolificans* is considered to be resistant to all triazoles and echinocandins [23], whereas *S. apiospermum* appears to be susceptible to extended-spectrum triazoles (e.g., voriconazole and posaconazole). Husain et al. [45] noted that, in more recent years, these infections have been appearing later in the posttransplantation period (i.e., a median of 6 months after transplantation) and may be related to exposure to amphotericin B or triazole prophylaxis. However, prolonged survival, delays in onset of graft-versus-host disease, or other factors may be more important in the later occurrence of these infections. Because these infections are so rare, we are unlikely to tease out the relative importance that increasing amounts of antifungal prophylaxis will have on the incidence of these infections.

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