# Invasive Fungal Pathogens: Current Epidemiological Trends

**Michael A. Pfaller,[1] Peter G. Pappas,[2] and John R. Wingard[3]**

[1]Departments of Pathology and Epidemiology, Medical Microbiology Division, Roy J. and Lucille A. Carver College of Medicine and College of Public Health, University of Iowa, Iowa City; [2]Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham; and [3]Blood and Marrow Transplantation Program, Department of Medicine, Division of Hematology/Oncology, Shands Cancer Center, University of Florida, Gainesville

**Patient characteristics, antifungal prophylaxis, and other factors appear to have contributed to a change in the spectrum of invasive fungal pathogens. Infections with *Candida glabrata, Aspergillus terreus,* and non-*Aspergillus* moulds appear to be on the rise, at least among certain populations. These species are resistant or less susceptible to some commonly used antifungal agents. Non-*Aspergillus* moulds are particularly lethal. This article reviews the spectrum of invasive mycoses and risk factors for infection with these pathogens.**

The frequency of invasive, opportunistic mycoses has increased significantly over the past 2 decades [1–5]. This increase in infection is associated with excessive morbidity and mortality [2, 5–11] and is directly related to the increasing numbers of patients who are at risk for the development of serious fungal infections, including patients undergoing blood and marrow transplantation (BMT), solid-organ transplantation, and major surgery (especially gastrointestinal surgery); patients with AIDS, neoplastic disease, and advanced age; patients receiving immunosuppressive therapy; and premature infants [2–5, 11–16]. Given the complexity of the population of patients who are at risk for infection and the diverse and increasing array of fungal pathogens (see table 1 of Alexander and Pfaller [17]), opportunistic mycoses pose considerable diagnostic and therapeutic challenges.

The most well-known causes of opportunistic mycoses include *Candida albicans, Cryptococcus neoformans,* and *Aspergillus fumigatus* [1, 4–6, 18, 19]. The estimated annual incidence of invasive mycoses due to these pathogens is 72–228 infections per million population for *Candida* species, 30–66 infections per million population for *C. neoformans,* and 12–34 infections per million population for *Aspergillus* species [10, 11, 18, 20, 21]. In addition to these agents, the growing list of "other" opportunistic fungi is of increasing importance [1] (see table 1 of Alexander and Pfaller [17]). New and "emerging" fungal pathogens include species of *Candida* and *Aspergillus* other than *C. albicans* and *A. fumigatus,* opportunistic yeastlike fungi (e.g., *Trichosporon* and *Rhodotorula* species), the Zygomycetes, hyaline moulds (e.g., *Fusarium* and *Scedosporium* species), and a wide variety of dematiaceous fungi [1, 22].

Infections caused by these organisms range from catheter-related fungemia and peritonitis, to more localized infections (e.g., those involving the lungs, skin, and paranasal sinuses), to widespread hematogenous dissemination [1, 23]. Many of these fungi were previously thought to be nonpathogenic and are now recognized causes of invasive mycoses in immunocompromised patients. Some of these organisms are inherently resistant to standard azole, polyene, or echinocandin therapy and may require the use of alternative antifungal agents in addition to surgical management and reversal of the underlying impairment of host defenses.

This article reviews selected aspects of the epidemiological profiles of the invasive mycoses and risk factors for infection with various fungal pathogens. The

Reprints or correspondence: Dr. Michael A. Pfaller, Medical Microbiology Div., C606 GH, Dept. of Pathology, University of Iowa College of Medicine, Iowa City, IA 52242 (michael-pfaller@uiowa.edu).

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susceptibility of pathogens to antifungal agents is also discussed. Infections due to the endemic fungi and *Cryptococcus* species are not considered in this review.

## *CANDIDA* SPECIES INFECTION

It is clear that the most important group of opportunistic fungal pathogens are the *Candida* species [1, 6, 11, 18, 22, 24–26]. *Candida* species account for 8%–10% of all nosocomial bloodstream infections (BSIs) and occur at a rate of 6–23 infections per 100,000 persons annually in the United States [2, 3, 6, 10, 11, 18, 20, 21, 26–29]. Between 1980 and the present, the frequency of *Candida*-associated BSI has increased steadily in hospitals of all sizes and in all age groups throughout the world [2, 6, 18, 26–38]. Notably, *Candida* species remain the most common fungal pathogens in intensive care unit (ICU), solid-organ transplantation, and BMT patient populations (figure 1) [2, 3, 6, 39]. The major concern with invasive candidiasis is that it is associated with an excess attributable mortality rate of 10%–49% [7, 9, 11, 40] and an excess length of hospital stay of 3–30 days [7, 9, 11, 40]. Furthermore, the excess cost attributable to candidemia in the United States approaches 1 billion dollars per year [9, 11, 41–43].

Although >100 species of *Candida* have been described, only a few species have been implicated in clinical infections. *C. albicans* is the species most commonly recovered from clinical material and generally is responsible for 90%–100% of mucosal infections and for 50%–70% of episodes of candidemia [2, 3, 6, 18, 27, 44–46].

Approximately 95%–97% of all *Candida*-associated BSIs are caused by 5 species: *C. albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis,* and *Candida krusei* [1, 2, 6, 18]. Among these common species, only *C. glabrata* can be said to be truly "emerging" as a cause of BSI, because, in part, of its intrinsic and acquired resistance to azoles and other commonly used antifungal agents [1, 3, 18, 25, 27, 44–47]. Specific aspects of each of these species will be addressed below.

The remaining 3%–5% of *Candida*-associated BSIs are caused by 12–14 different species, including *Candida lusitaniae, Candida guilliermondii,* and *Candida rugosa* (see table 1 of Alexander and Pfaller [17]) [1, 22, 48]. Although these species must be considered "rare" causes of candidiasis, several have been observed to occur in nosocomial clusters or to exhibit innate or acquired resistance to one or more established antifungal agents [1, 22, 49–55].

**C. albicans.** Among the various species of *Candida* capable of causing human infection, *C. albicans* predominates. Superficial infections of genital, oral, and cutaneous sites almost always (>90% of cases) involve *C. albicans.* A wider array of *Candida* species causes BSI, and, although *C. albicans* predominates, the frequency with which this and other species of *Candida* are recovered from blood samples varies according to the geographic setting [3, 12, 25, 27, 44, 46, 54, 56–59]. Globally, a decreasing trend in the rate of *C. albicans* isolation (overall decrease, 10%–11%) was noted over a 6.5-year period (1997–2003) among 127 sentinel surveillance sites in 39 countries [54]. Notably, only 44% of cases of *Candida*-associated BSI in Latin America were due to *C. albicans,* compared with 62% of cases of BSI in Europe [54, 59]. BSIs due to *C. albicans* have been shown to occur less frequently with increasing patient age [1, 26, 27, 44], after exposure to azole antifungals [12, 24, 56–58, 60], and in the ICU setting [3]. Although *C. albicans* is usually considered to be an endogenous pathogen (i.e., infection arises from the patient's own flora), exogenous transmission from patient to patient via the hands of health care personnel is well documented [25, 61].

**C. glabrata.** *C. glabrata* has emerged as an important and potentially resistant opportunistic fungal pathogen [1, 3, 12, 18, 22, 24–27, 44, 46, 57, 62–64]. Trick et al. [3] have demonstrated that, among the *Candida* species, *C. glabrata* alone has increased as a cause of BSI in US ICUs since 1993. On a global scale, the frequency of *C. glabrata* as a cause of BSI varies from 22% in North America to 4%–6% in Latin America [29, 54, 64]. Within the United States, the proportion of fungemias due to *C. glabrata* has been shown to vary from 11% to 37% across the 9 US Bureau of the Census Regions [29] and from 9% to 29% within a single institution over the course of an 8-year period [63]. Although the frequency of *C. glabrata* as a cause of BSI has not changed substantially in North America over the past 4 years, its frequency has decreased from 12.3% to 8.8% in Europe and from 10.2% to 4.7% in Latin America [54]. Numerous studies have shown that both colonization and infection with *C. glabrata* are rare among infants and children and increase significantly with increasing patient age [1, 14, 18, 26, 28, 44, 63, 65, 66]. Importantly, more than one-third of *Candida*-associated BSIs among patients >60 years of age are due to *C. glabrata* [27, 28, 63]. This dramatic variation in the incidence of *C. glabrata* fungemia appears to be multifactorial [63, 67]. It has been shown that the prevalence of this species is potentially related to disparate factors, including geographic characteristics [29, 54, 64], age [28, 63], characteristics of the

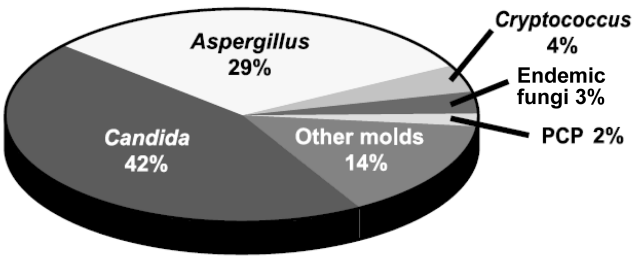


**Figure 1.** Pathogens causing invasive fungal infections among solid-organ and hematopoietic stem cell transplant recipients. Data are from Pappas et al. [39]. PCP, *Pneumocystis jiroveci (carinii).*

patient populations studied [12, 24, 46], and use of fluconazole [12, 24, 46]. Because *C. glabrata* is relatively resistant to fluconazole, the frequency with which it causes BSI has important implications for therapy [63].

**C. parapsilosis.** *C. parapsilosis* is the second most common species of *Candida* recovered from blood cultures in Europe (12%) and the Asia-Pacific region (17%) and has increased in prevalence from 14% to 20% ($P = .01$) in Latin America over the past 4 years [54]. It is an important species to consider for hospitalized patients with vascular catheters [68–71]. *C. parapsilosis* is the most common species found on the hands of health care workers [72], and it affects critically ill neonates and ICU patients likely because of its association with parenteral nutrition and central venous catheters [68–71]. *C. parapsilosis,* more so than other species of *Candida,* tends to form extensive biofilms on the surface and lumens of catheters and other implanted devices [69, 73], which has been specified as a reason why patients with *C. parapsilosis*–infected catheters should have the device removed [68, 70]. Biofilm-forming organisms have been shown to be completely resistant to antifungal agents [69]. Finally, *C. parapsilosis* has been implicated in a number of nosocomial outbreaks of catheter-associated fungemia, thus underscoring the importance of hand hygiene and proper catheter care [68, 70, 71].

**C. tropicalis.** *C. tropicalis* has long been considered as an important cause of fungemia and invasive candidiasis in patients with cancer, especially leukemia, and in BMT recipients [12, 24, 67, 74, 75]. Among patients with neutropenia who are found to be colonized with *C. tropicalis,* as many as 60%–80% eventually develop invasive infection [75–77]. As such, *C. tropicalis* has been considered to exhibit increased virulence, especially in those individuals with disrupted mucosal integrity [74, 75, 78]. Given these considerations, prophylaxis treatment with fluconazole for patients with neutropenia has been used in an effort to decrease infections due to *C. tropicalis,* as well as *C. albicans* [12, 24, 46]. *C. tropicalis* has remained highly susceptible to fluconazole, and prophylaxis with fluconazole in patients with neutropenia has proven to be protective against the development of *C. tropicalis* infections [12, 24, 74]. Although *C. tropicalis* is only the fourth most frequent *Candida*-associated BSI isolate recovered in North America (7% of BSIs), it ranks second in Latin America (20%) and is more common than *C. glabrata* (13% vs. 10%, respectively) in the Asia-Pacific region [29, 54, 59].

**C. krusei.** *C. krusei* causes 2%–4% of all *Candida*-associated BSIs [1, 26, 29] and is best known for its propensity to emerge in settings where fluconazole is used for prophylaxis [1, 12, 24, 46, 57]. Similar to *C. tropicalis* infections, *C. krusei* infections occur most often in patients with neutropenia, and colonization of patients is often predictive of subsequent BSI [12, 24, 46, 57, 76, 77, 79, 80]. Although *C. krusei* is best known for resistance to fluconazole, it may also exhibit decreased susceptibility to amphotericin B and flucytosine [1, 18, 46], further complicating therapy [46]. BSI due to *C. krusei* is associated with a high mortality rate (80% crude mortality and 40% attributable mortality), possibly related to its poor response to standard antifungal therapy [46, 79]. It should be noted that colonization and infection with *C. krusei* were apparent in certain medical centers well in advance of the use of fluconazole [67, 75, 81, 82].

***Risk factors.*** Certain hospitalized individuals are well known to be at risk for acquiring candidemia during hospitalization as a result of their underlying medical condition, including patients with hematologic malignancies or neutropenia, patients undergoing gastrointestinal surgery, premature infants, and elderly persons (i.e., those >70 years of age) [6, 12, 13, 18, 24, 25, 46, 66]. Within these high-risk groups, additional risk factors have been recognized, and these specific exposures have not changed significantly during the past 2–3 decades [83–86]. The presence of vascular catheters, exposure to broad-spectrum antimicrobial agents, renal failure, mucosal colonization with *Candida* species, prolonged ICU stay, and receipt of total parenteral nutrition are all recognized to increase the risk for nosocomial candidemia [3, 6, 12, 13, 25, 26, 46, 66, 84, 86, 87]. Compared with control subjects without the specific risk factors or exposures, these already high-risk patients have a likelihood of contracting candidemia in the hospital setting that is ~2 times greater for each class of antimicrobial agents received, 7 times greater for patients with a central venous catheter, 10 times greater if a *Candida* species is colonizing other anatomical sites, and 18 times greater for patients who have undergone acute hemodialysis [13, 85, 86, 88]. Hospitalization in the ICU setting provides the opportunity for transmission of *Candida* species among patients and has been shown to be an additional independent risk factor [13, 25, 66, 88].

The available epidemiologic data indicate that 5–10 of every 1000 high-risk patients exposed to the above risk factors will contract BSI due to *Candida* species [3, 13, 18, 41, 43, 88]. Approximately 49% of these patients will die as a result of their infection, 12% will die of their underlying disease, and 39% will survive hospitalization [7, 85, 88]. This picture has not changed from and may even be worse than that seen in the mid-1980s [40, 83, 84]. The outcome for almost half of those patients with candidemia could be improved by more effective means of prevention, diagnosis, and therapy [83, 88]. Clearly, the most desirable of these measures is prevention, which is best approached by rigorous control of exposures—in particular, by limiting the use of broad-spectrum antibiotics, improving catheter care, and adhering to infection control practices [13, 83]. Risk stratification of patients has been suggested as an efficient way to identify patients for early diagnostic and

therapeutic interventions and, thus, to reduce infection-related deaths [88, 89].

***Mortality.*** The consequences of candidemia in hospitalized patients are severe. Patients with candidemia have been shown to be at a 2-fold greater risk of death during hospitalization than are patients with noncandidal BSI [90]. Among all patients with nosocomial BSI, candidemia was found to be an independent predictor of death during hospitalization [90, 91]. More recently, risk factors for mortality among 1593 patients with candidemia were an APACHE II score >18 ($P < .001$), cancer ($P = .002$), the presence of a urinary catheter ($P = .004$), male sex ($P = .004$), the use of corticosteroids ($P < .001$), and the presence of an arterial catheter ($P < .001$) [6]. Although estimates of mortality due to candidemia may be confounded by the serious nature of the underlying disease in many of these patients, matched cohort–based and population-based studies have confirmed that the mortality rate directly attributable to candidemia is quite high, ranging from 10% to 49% [6, 7, 9, 11, 40, 84]. Notably, the excess mortality attributable to candidemia has not decreased significantly over the past 2 decades, despite the introduction of new antifungal agents with good activity against most species of *Candida* [7, 40, 83, 84]. This failure to affect overall mortality due to candidemia is likely due to delays in administration of effective antifungal therapy to patients with infection and to administration of therapy for an insufficient duration [9, 92]. A recent study at a tertiary care medical center identified failure to administer appropriate antifungal therapy within 12 h of drawing the first positive blood culture as an independent predictor of hospitalization-associated mortality [92]. Likewise, a population-based active surveillance study conducted in Connecticut and in the Baltimore metropolitan area between 1998 and 2000 found a significant difference in mortality attributable to candidemia between patients receiving systemic antifungal therapy for at least 7 days after the first positive blood culture and patients receiving therapy for <7 days (11%–16% vs. 31%–41%, respectively) [9]. Thus, the ability to affect mortality due to candidemia depends on administration of appropriate antifungal therapy (i.e, the right drug and dose) early during the course of the infection and for an adequate duration. Clearly, this has important implications not only for diagnostic testing but also for consideration of prophylactic and empirical treatment strategies.

***Prophylaxis and empirical therapy.*** Given the substantial excess mortality due to candidemia and the difficulties encountered in administering early and effective antifungal therapy [84, 92], it is clear that prevention is primary [83]. Although the urge to administer antifungal prophylaxis to any and all high-risk patients is strong, there are 3 important strategies that should form the bedrock of any approach to prevent morbidity and mortality resulting from nosocomial candidemia [83]: (1) improved hand hygiene, (2) optimal catheter care, and (3) prudent antimicrobial use. Once these measures are in place, one can begin to consider the use of prophylactic and presumptive (empirical) antifungal therapy to decrease mortality and morbidity resulting from nosocomial candidemia.

Antifungal prophylaxis has been proven to be effective in decreasing mucosal and invasive candidiasis in patients with neutropenia [24]. Administration of fluconazole (400 mg/day) during neutropenia has proven to be effective in decreasing the number of infections due to *C. albicans, C. tropicalis,* and *C. parapsilosis* (figure 2) [12, 24, 46]. This practice has resulted in a significant decrease in the incidence of candidemia and associated mortality, despite selecting for fluconazole-resistant strains of *C. glabrata* and *C. krusei* [12, 24]. Unfortunately, the data are less compelling for nonneutropenic ICU patients. Placebo-controlled trials have demonstrated a reduction in invasive candidiasis among surgical ICU patients who receive fluconazole prophylaxis [60, 93, 94]; however, those studies were conducted at single institutions with high baseline rates of infections. The potential for drug toxicity, drug interactions, and the emergence of antifungal-resistant *Candida* species are all arguments against a blanket recommendation to use prophylactic antifungal agents for nonneutropenic ICU patients. A clear example of the problems that may be encountered was described by Sarvikivi et al. [71], who found that the emergence and subsequent transmission of a fluconazole-resistant strain of *C. parapsilosis* was associated with the use of fluconazole prophylaxis in a neonatal ICU. The use of antifungal prophylaxis in the ICU population must be institution specific and can be justified only if (1) major and concerted efforts have been made to improve hand hygiene, catheter care, and antimicrobial use practices; (2) the rate of nosocomial candidemia remains high, despite these efforts; and (3) a local observational study can define a subpopulation within the ICU with a cumulative incidence of invasive candidiasis approaching or exceeding 10% [83, 88].

It is now apparent that initial empirical treatment of can-

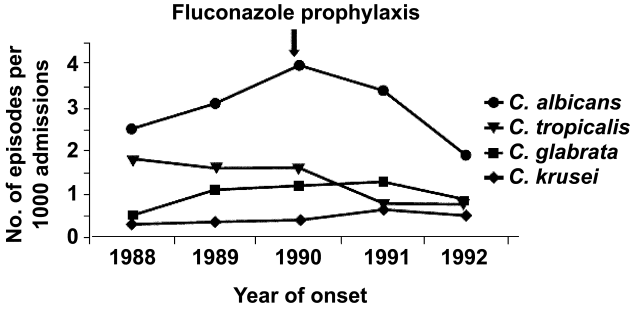


**Figure 2.** Episodes of hematogenous candidiasis, by *Candida* species, at M. D. Anderson Cancer Center (Houston, TX), 1988–1992. Adapted with permission from Abi-Said et al. [12].

**Table 1. Antifungal susceptibility of *Candida* species.**

| Antifungal agent | Percentage of strains susceptible to each agent[a] | | | | |
|---|---|---|---|---|---|
| | *C. albicans* | *C. glabrata* | *C. parapsiolsis* | *C. tropicalis* | *C. krusei* |
| Amphotericin B | 100 | 75[b] | 97 | 99 | 8[b] |
| Flucytosine | 97 | 99 | 99 | 93 | 6[c] |
| Fluconazole | 99 | 54[d] | 96 | 99 | 0[e] |
| Itraconazole | 99 | 77[d] | 99 | 99 | 94 |
| Posaconazole | 99 | 86 | 100 | 100 | 99 |
| Voriconazole | 100 | 92 | 100 | 99 | 100 |
| Caspofungin | 100 | 100 | 97 | 99 | 99 |
| Micafungin | 99 | 100 | 100 | 100 | 100 |

**NOTE.** All organisms are susceptible unless otherwise noted. Data are from [26, 29, 44, 95–99].

[a] Susceptibility is defined as an MIC of ⩽8 μg/mL for fluconazole, ⩽4 μg/mL for flucytosine, or ⩽1 μg/mL for all other agents.

[b] Intermediately susceptible.

[c] Intermediately resistant.

[d] Susceptible in a dose-dependent fashion.

[e] Resistant.

didemia is often delayed or inappropriate and that this delay is associated with a greater risk of hospitalization-associated mortality [9, 92]. One study found that 95% of patients with candidal BSI received inappropriate initial treatment [92]. Specifically, the most common cause of inappropriate treatment for candidemia was omission of initial empirical therapy. Thus, clinicians should strive to administer appropriate initial antifungal therapy to patients at the earliest time possible after suspecting the presence of infection.

Early empirical therapy should be guided by an understanding of the most important risk factors for candidemia [89]. Such an approach has been outlined by Wenzel and Gennings [88], who demonstrated that, by using specific risk factors and the known background attack rate for *Candida*-associated BSI in a given ICU, one can determine risk estimates for candidemia. They suggested that this approach would be an efficient way to select patients who are at high risk for candidemia for early treatment with effective agents. This approach should be applicable to both empirical and prophylactic strategies, as well as diagnostic testing strategies, but will require further clinical studies to determine the impact on the rate of candidemia and directly associated deaths.

***Antifungal susceptibility.*** Among the 5 most common species of *Candida, C. albicans, C. parapsilosis,* and *C. tropicalis* remain reliably susceptible to polyenes, flucytosine, the azoles, and the echinocandin antifungal agents (table 1) [18, 26, 28, 29, 44, 46, 54, 59, 95–99]. Although *C. parapsilosis* is known to exhibit higher MICs than other species of *Candida* for the echinocandins (modal MIC, 0.25–0.5 μg/mL vs. 0.06–0.12 μg/mL, respectively), >99% of all clinical BSI isolates are susceptible to echinocandins at concentrations of 1–2 μg/mL, which are easily achieved with standard dosing, and this species generally responds well clinically to echinocandin therapy [59, 95, 97, 100]. It should be noted that, although in vitro susceptibility testing methods for echinocandins and *Candida* species have now been standardized [59, 97, 101, 102] and can reliably differentiate strains with decreased susceptibility due to mutations in the *FKS1* gene from normally susceptible or wild-type strains [97, 101, 103, 104], MIC interpretive breakpoints have not yet been established for clinical use [100].

As noted above, *C. glabrata* is inherently less susceptible to fluconazole and amphotericin B than are most other species of *Candida* [1, 18, 26, 29, 44, 46, 54, 64, 96, 98, 99]. Although both voriconazole and posaconazole are active against the vast majority of *C. glabrata* isolates, cross-resistance within the azole class is well documented for this species [1, 95, 96, 98]. *C. glabrata* is very susceptible to the fungicidal activity of the echinocandins [59, 95, 97, 102, 104]. In addition to its intrinsic resistance to fluconazole, *C. krusei* shows decreased susceptibility to both amphotericin B and flucytosine [1, 98]. In contrast, this species is very susceptible to both the extended-spectrum triazoles (posaconazole and voriconazole) and the echinocandin antifungal agents [1, 59, 96–98, 102, 104].

## *ASPERGILLUS* SPECIES

Aspergillosis encompasses a broad spectrum of diseases caused by members of the genus *Aspergillus* [4, 5, 19, 105]. Exposure to *Aspergillus* species in the environment may cause allergic reactions in hypersensitized hosts or destructive, invasive pulmonary and disseminated disease in highly immunosuppressed individuals [4, 5, 19]. Although ~19 species of *Aspergillus* have been documented as agents of human disease, the majority of infections are caused by *A. fumigatus, Aspergillus flavus, Aspergillus niger,* and *Aspergillus terreus* [4, 105].

*Aspergillus* species are common throughout the world. Their

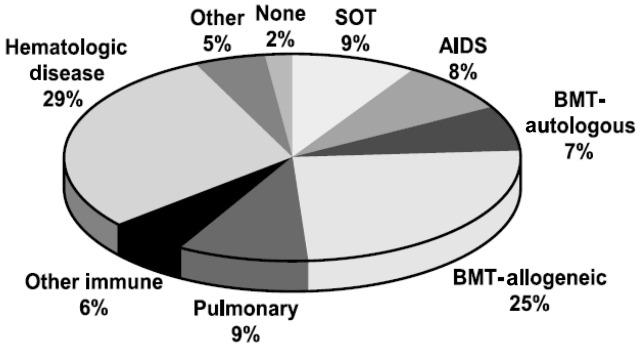


**Figure 3.** Underlying disease in 595 patients with invasive aspergillosis [19]. BMT, bone marrow transplant; SOT, solid-organ transplant.

conidia are ubiquitous in air, soil, and decaying matter. Within the hospital environment, *Aspergillus* species may be found in air, showerheads, water storage tanks, and potted plants [106, 107]. As a result, the conidia are constantly being inhaled. The type of host reaction, the associated pathologic findings, and the ultimate outcome of infection depend more on host factors than on the virulence or pathogenicity of the individual *Aspergillus* species [4, 5, 19, 105, 108, 109].

***Risk factors.*** Invasive aspergillosis (IA) affects a more narrow range of patients than does invasive *Candida* infection. Nearly two-thirds (61%) of patients with IA have underlying hematological diseases (including hematological cancers) or have undergone BMT (figure 3) [19].

Multiple analyses have examined which patients within these groups face the highest risk of IA. Risk factors include grade III–IV graft-versus-host disease, receipt of steroids, prolonged or repeated episodes of profound neutropenia, age >40 years, receipt of BMT from an HLA-mismatched or unrelated donor, and infliximab therapy [5, 8, 19, 47, 110]. In one analysis, more than half the allogeneic BMT recipients who developed invasive mycoses due to pathogens other than *A. fumigatus* had received antifungal prophylaxis with amphotericin B. Among these were species of *Aspergillus (A. terreus* and *A. ustus)* and other moulds *(Scedosporium apiospermum)* with demonstrated in vitro resistance to amphotericin B. The authors suggested that amphotericin B prophylaxis may have led to emergence of resistant organisms [4].

In high-risk patients, a respiratory tract sample (e.g., sputum or bronchoalveolar lavage) that is culture positive for *Aspergillus* species is associated with invasive disease. A positive culture was associated with IA in nearly two-thirds of allogeneic BMT recipients (64%) and patients with neutropenia (64%) and in half of patients with hematological cancers (50%) [105].

***Mortality.*** IA is associated with a high mortality rate. In one series of 1209 aspergillosis cases in 24 medical centers, 62% of patients with *Aspergillus* species infection had died within 3 months of receiving a positive culture result [105]. Mortality rates as high as >85% have been reported for IA [19]. Infection with any invasive mould (*Aspergillus* or *Fusarium* species or Zygomycetes) is highly lethal among hematopoietic stem cell transplant (HSCT) recipients, with 80% of patients dead 1 year after infection [5]. Although rare, invasive fungal infections due to *Aspergillus* species and the Zygomycetes may occur in individuals with late-stage AIDS (stage III) [111]. Infection may be indolent or aggressive. Disseminated infection may occur and generally is associated with a high mortality rate (~80%).

Analysis of the TRANSNET database yields risk factors for death with IA in the transplant population ($n = 244$ patients with IA). Persons who have undergone HSCT are more likely to die of IA than are those who have undergone solid-organ transplantation (mortality rate, 68% vs. 41%; $P < .0001$) [112]. Other risk factors for death due to IA include CNS disease (88% vs. 53%; $P = .0005$), proven (rather than possible) IA (68% vs. 49%; $P = .0058$), and methylprednisolone use within 9 days of diagnosis ($P = .0008$) [112].

***Antifungal susceptibility.*** Specific antifungal therapy for aspergillosis often involves the administration of amphotericin B or one of its lipid-based formulations [4, 5, 19]. Although the vast majority of *Aspergillus* species remain susceptible to this class of antifungal agents, it is important to realize that *A. terreus* is considered to be resistant to amphotericin B, and infections with this species should be treated with an alternative agent (figure 4) [1, 22, 23, 114–117]. The introduction of voriconazole provides a treatment option that has excellent activity against all *Aspergillus* species (figure 4) and that is more efficacious and less toxic than amphotericin B [109, 118]. Likewise, caspofungin, posaconazole, and itraconazole show excellent activity against *Aspergillus* species, including *A. terreus* (figure 4) [1, 113].

Although beyond the scope of this review, concomitant efforts to decrease immunosuppression and reconstitute host immune defenses are important components of treatment for IA [4, 5, 19, 22, 23, 109, 119]. The availability of a wide range of recombinant cytokines (e.g., IFN-$\gamma$ and colony-stimulating fac-

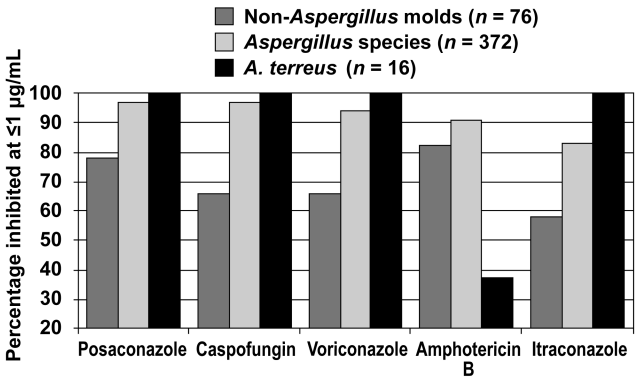


**Figure 4.** In vitro susceptibility of clinical mould isolates [1, 113]. Used with permission from Pfaller and Diekema [1].

tors) that exert their effects indirectly through leukocyte activation, rather than directly on the fungus, hold great promise as adjunctive therapies for IA [109, 119]. Immunotherapy is designed to increase the number of phagocytic cells and shorten the duration of neutropenia (e.g., colony-stimulating factors and granulocyte transfusions), modulate the actions of those cells at the site of infection, and activate the fungicidal activity of phagocytes to kill fungal cells more efficiently (e.g., colony-stimulating factors, IFN-$\gamma$, and toll-like receptor activation) [109, 119]. Additional adjunctive measures used in the treatment of IA include combinations of antifungals [120] and surgical resection, if possible, of involved areas. Although these measures (i.e., immunomodulation and combination antifungal therapy) are now widely applied in the management of difficult invasive fungal infections, for the most part, they remain to be fully studied [109, 119, 120].

## NON-*ASPERGILLUS* INVASIVE MOULDS

A large ($N = 5589$) retrospective (1985–1999) review of records at Fred Hutchinson Cancer Research Center (Seattle, WA) revealed that the 3 most common non-*Aspergillus* moulds causing invasive fungal infection among HSCT recipients were *Fusarium* and *Scedosporium* species and Zygomycetes (figure 5) [5]. Although infections caused by these fungi are relatively rare, they appear to be increasing in incidence [1, 4, 5, 22, 23]. Most disseminated infections are thought to be acquired by inhalation of spores or by the progression of previously localized cutaneous lesions [23]. These organisms tend to cause infections in patients with neutropenia; the infections often are disseminated in nature and are almost uniformly fatal in the absence of immune reconstitution [4, 5]. Both *Fusarium* and *Scedosporium* species are capable of adventitious conidiation (i.e., generation of spores in tissue), with concomitant hematogenous dissemination, positive blood cultures, and multiple cutaneous lesions [1, 23]. Overall, these non-*Aspergillus* moulds are less susceptible to the available systemically active antifungal agents than are the *Aspergillus* species (figure 4) [1, 113]. Voriconazole has been approved by the US Food and Drug Administration for the treatment of serious infections caused by *Fusarium* species and by *S. apiospermum* in patients who are intolerant of or refractory to other antifungal agents [121].

**Fusarium *species.*** Fusariosis has been recognized with increasing frequency among immunocompromised patients, especially patients with hematologic malignancies and recipients of allogeneic HSCT [122, 123]. The most common species isolated from clinical specimens include *Fusarium moniliforme, Fusarium solani,* and *Fusarium oxysporum* [122]. The hallmark of disseminated fusariosis is the appearance of multiple purpuric cutaneous nodules with central necrosis [122–124]. Biopsy of these nodules generally reveals branching, hyaline, and septate hyphae invading dermal blood vessels. In contrast to patients with IA, ~75% of patients with fusariosis will have positive blood cultures [23]. Mortality is high, with only 13%–21% of patients alive at 90 days after diagnosis [123]. Persistent neutropenia is both a risk factor for the development of fusariosis and an important (negative) prognostic factor [123]. Both persistent neutropenia and corticosteroid therapy are known to negatively influence the outcome of patients with cancer with fusariosis [123].

*Fusarium* species often appear to be resistant to amphotericin B in vitro [1, 113], and breakthrough infections occur frequently in patients treated with this agent [23, 121, 122]. Among the new triazoles, only modest activity is seen in vitro [1, 113]; however, voriconazole has been used successfully in some patients with amphotericin B–refractory fusariosis [121]. The echinocandins are not active against *Fusarium* species [113]. Primary therapy with either voriconazole or a lipid formulation of amphotericin B plus vigorous efforts at immune reconstitution is recommended at this time [23, 122].

***Zygomycetes.*** Zygomycosis is a sporadic disease that occurs worldwide and is caused by fungi of the class Zygomycetes and the order Mucorales. *Rhizopus oryzae (arrhizus)* is the most common cause of zygomycosis; however, additional species of *Rhizopus, Rhizomucor, Absidia,* and *Cunninghamella* are known to cause invasive disease in hospitalized individuals [125–127]. Infections due to the Zygomycetes are rare, occurring at an annual rate of 1.7 infections per million population in the United States [21]. In the past decade, however, zygomycosis has emerged as an increasingly important mycosis, particularly among HSCT recipients and patients with hematologic malignancies (figure 6) [1, 110, 126, 128].

The agents of zygomycosis are ubiquitous in soil and decaying vegetation, and infection may be acquired by inhalation, ingestion, or contamination of wounds with sporangiospores from the environment [127]. As with *Aspergillus* species, nosocomial spread of Zygomycetes may occur by way of air-conditioning

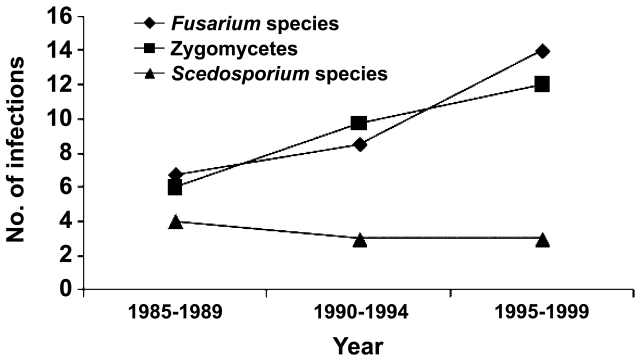


**Figure 5.** Changing frequency of non-*Aspergillus* moulds in blood and marrow transplantation recipients at Fred Hutchinson Cancer Research Center (Seattle, WA), 1985–1999. Used with permission from Marr et al. [5].

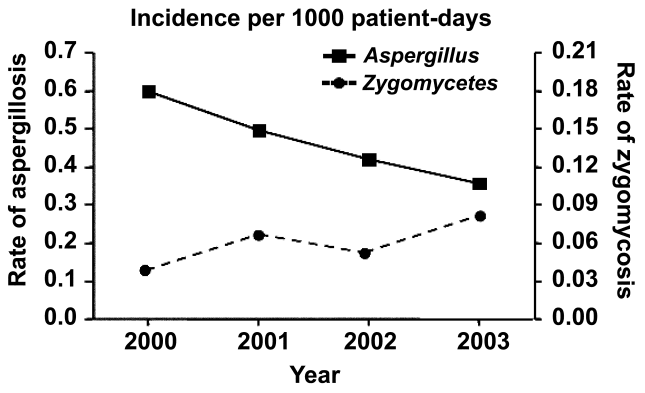


**Figure 6.** Changing spectrum of *Aspergillus* and Zygomycetes at M. D. Anderson Cancer Center (Houston, TX). Used with permission from Kontoyiannis et al. [110].

systems, particularly during construction [125–127]. Focal outbreaks of zygomycosis have also been associated with the use of contaminated adhesive bandages or tape in surgical wound dressings, resulting in primary cutaneous zygomycosis [125, 127].

In addition to causing infection in immunocompromised patients, the Zygomycetes may also cause lethal infections in a broader and more heterogeneous population, such as patients with diabetes, patients receiving deferoxamine therapy, injection drug users, and patients with no apparent immune impairment [126]. Invasive zygomycosis is clinically similar to aspergillosis and is marked by angioinvasion and tissue infarction [127]. The most common types of infection are sinus (39%), pulmonary (24%), and cutaneous (19%) [126]. Dissemination develops in 23% of cases, and the associated mortality rate is 96% [126]. Significant risk factors for mortality include disseminated disease, renal failure, and infection with *Cunninghamella* species [126].

Risk factors for zygomycosis include prior corticosteroid and deferoxamine therapy, diabetic ketoacidosis, renal failure, hematologic malignancy, myelosuppression, and exposure to hospital construction activity [125–127]. Recently, exposure to voriconazole, an agent that is not active against the Zygomycetes, has been shown to be a risk factor for zygomycosis in patients with cancer [110, 128].

Most of the Zygomycetes appear to be quite susceptible to amphotericin B in vitro and are generally not susceptible to the triazoles and echinocandins [1, 113]. Among the extended-spectrum triazoles, posaconazole stands apart from voriconazole in that it appears to be active against most of the Zygomycetes, both in vitro and in vivo [1, 113, 129–131]. A recent case series of 24 patients with zygomycosis suggests that posaconazole appears to be promising (79% complete or partial response) as an oral therapy for patients who received surgery required for control of their underlying illness [131]. In contrast, voriconazole is inactive against the Zygomycetes [1, 113], and breakthrough zygomycosis has been reported in patients receiving voriconazole prophylaxis [110, 128, 132, 133].

**Scedosporium *species.*** Within the genus *Scedosporium, S. apiospermum* (teleomorph *Pseudallescheria boydii)* and *Scedosporium prolificans* represent 2 important antifungal-resistant opportunistic pathogens [1, 23]. *S. apiospermum* may be isolated from soil and is an occasional cause of mycetoma; however, it is also a cause of serious disseminated and localized infection in immunocompromised patients. In addition to widespread disseminated disease, *S. apiospermum* has been reported to cause corneal ulcers, endophthalmitis, sinusitis, pneumonia, endocarditis, meningitis, arthritis, and osteomyelitis [22, 23, 134–136]. *S. apiospermum* is indistinguishable from *Aspergillus* species and other agents of hyalohyphomycosis on histopathologic examination, which further emphasizes the need for culture and mycological identification of the fungus. Such distinction is clinically important, because *S. apiospermum* is resistant to amphotericin B but is susceptible to voriconazole and posaconazole [1, 113, 135–138].

*S. prolificans* causes bone and soft-tissue infections in immunocompetent individuals and deeply invasive and disseminated infections in immunocompromised patients [23, 134]. *S. prolificans* is considered to be resistant to virtually all the systemically active antifungal agents, including the extended-spectrum triazoles and the echinocandins [1, 138]. A single patient with disseminated *S. prolificans* infection was successfully treated with a combination of voriconazole and terbinafine (an inhibitor of fungal squalene epoxidase with broad antifungal activity), in addition to aggressive surgical debridement [139].

A recent review of infections due to *S. apiospermum* and *S. prolificans* in transplant recipients found that the majority of infections (53%–69%) were disseminated and that HSCT recipients were more likely than solid-organ transplantation recipients to have infections caused by *S. prolificans* [134]. The mortality rate among transplant recipients with scedosporiosis was 58%. The presence of disseminated infection predicted lower chances of survival, and treatment with voriconazole, versus amphotericin B, and receipt of adjunctive surgery as treatment predicted a better chance of survival.

## SUMMARY

*Candida* and *Aspergillus* species remain the most common causes of invasive fungal infections, but non-*albicans Candida* species and non-*fumigatus Aspergillus* species are emerging more frequently and often are resistant to fluconazole and amphotericin B, respectively. Highly lethal non-*Aspergillus* moulds, such as *Fusarium* and *Scedosporium* species and Zygomycetes, also are surfacing, especially among patients with leukemia and BMT recipients. In the case of Zygomycetes, emergence has been linked to voriconazole prophylaxis.

Risk factors for systemic *Candida* infection include the use

of central venous catheters, total parenteral nutrition, recent surgery, and receipt of immunosuppressive therapy [3, 13, 18]. Invasive aspergillosis disproportionately affects persons with hematological disease and patients who have undergone BMT [19]. Fusariosis and zygomycosis have been reported most frequently in these same populations [110, 122–124, 128, 132]. A high index of suspicion for fungal infection and for atypical species is prudent when treating patients in these risk groups.

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