Emerging Fungal Diseases

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The epidemiology of invasive fungal infection is evolving. Yeasts other than *Candida albicans* and molds other than *Aspergillus fumigatus* have emerged as significant causes of invasive mycoses in severely immunocompromised patients. Although, in some instances, these changes may be related to medical interventions, such as the use of antifungal agents in prophylaxis, in the majority of cases, they seem to be a consequence of changes in the host, such as more-severe immunosuppression or different types of immunosuppression impacting both risk periods and the infections that occur. These factors have altered the epidemiology of infection in organ transplant recipients, premature newborns, and critically ill patients. This review discusses the epidemiology of some fungal infections that have emerged in the past few years, with an emphasis on the potential factors associated with their emergence and on practical implications of these epidemiological changes.

The epidemiology of invasive fungal infection has changed during the past 20 years. The incidence has increased, and the population of patients at risk has expanded to include those with a broad list of medical conditions, such as solid-organ and hematopoietic stem cell transplantation (HSCT), cancer, receipt of immunosuppressive therapy, AIDS, premature birth, advanced age, and major surgery. Furthermore, the etiology of these infections has changed. In the 1980s, yeasts (particularly *Candida albicans*) were the most common causative agents of invasive mycoses. In recent years, molds have become more frequent in certain groups of patients, such as HSCT recipients, and, in patients in whom candidiasis is still the most frequent invasive mycosis, non-*albicans* species of *Candida* account for >50% of infections [1]. In addition, infections caused by other yeasts, such as *Trichosporon* species, have been reported [2]. Among molds, reports of aspergillosis caused by non-*fumigatus* species of *Aspergillus* [3], zygomycosis [4], and infection caused by hyaline and black molds have been increasing in number [5, 6]. The exact reasons for these changes are not completely clear. In some circumstances, they may be related to specific medical interventions, such as antifungal prophylaxis and the use of medical devices. However, in the majority of the cases, they seem to be a consequence of changes in the host, such as more-severe immunosuppression or different types of immunosuppression impacting both risk periods and the infections that occur [7].

The term "emerging infection" may be used to denote an infection that has newly appeared in the population or one that is rapidly increasing in incidence or geographic range [8]. In this review, we will discuss the epidemiology of some fungal infections that have emerged in the past few years, with an emphasis on the potential factors associated with their emergence and on practical implications of these epidemiological changes. A summary of the suggested therapy for these infections is shown in table 1.

EMERGING YEASTS: FUNGEMIA

As mentioned above, *C. albicans* has been regarded as the most common agent of invasive yeast infection. With the introduction and widespread use of fluconazole, the overall incidence of candidemia has decreased, with a reduction of infections caused by *C. albicans* and an increase of infections caused by *Candida glabrata* [9]. *C. glabrata* has emerged as the second-most common agent of candidemia in the United States since the early 1990s [10]. In addition, *C. glabrata* has been recently associated with oropharyngeal candidiasis in patients receiving radiotherapy for head and neck cancer [11]. A major problem with infection due to *C. glabrata* is its decreased susceptibility to fluconazole. With the newer azoles, cross-resistance is also a concern, because the main mechanism of resistance to fluconazole is the over-expression of multidrug efflux pumps [12]. In a large study that evaluated 610 isolates of *C. glabrata* ob-

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Table 1. Treatments of choice for emerging fungal infections.

Causative agent, by type	Treatment	Reference(s)
Yeasts		
Candida glabrata	Caspofungin	[47]
Candida rugosa	Fluconazole, amphotericin B[a]	[20, 48]
Trichosporon species	Fluconazole	[24]
Cryptococcus gattii	Amphotericin B, fluconazole	…
Molds		
Aspergillus terreus	Voriconazole	[37]
Zygomycetes	Amphotericin B at high doses, lipid amphotericin B, posaconazole	[49]
Fusarium species	Lipid amphotericin B, voriconazole	[50, 51]
Scedosporium apiospermum	Voriconazole, itraconazole	[52]
Scedosporium prolificans	Voriconazole	[52]

[a] On the basis of MICs, *C. rugosa* has a poor response to amphotericin B in an outbreak.

tained from patients from different parts of the world with invasive infections, the percentages of strains susceptible to posaconazole, ravuconazole, and voriconazole (with MICs of $\leqslant 1$ μg/mL) were 85.4%, 90.7%, and 92.8%, respectively. More importantly, among 46 fluconazole-resistant isolates of *C. glabrata,* only 13% were susceptible to voriconazole, 4% were susceptible to posaconazole, and 8.7% were susceptible to ravuconazole [13]. The potential for the emergence of voriconazole-resistant *C. glabrata* as a threat to people receiving voriconazole therapy is an issue that has been raised in a case study of breakthrough infections at a single health care center [14].

In some parts of the world, especially in Latin American countries, *Candida parapsilosis* and *Candida tropicalis* preempt *C. glabrata* as the second leading cause of candidemia [15]. Although reasons for the emergence of these organisms are not known, risk factors such as the use of intravenous catheters, contamination of infusate, and colonization of health care workers have been implicated in *C. parapsilosis* infection, instead of drug-induced selection pressure [16]. Geographical differences outline the complexity of epidemiology; multiple factors, including the specialties of regional medical centers, patterns of practice, and host factors, likely support the emergence of different *Candida* species as predominant pathogens. Data from preliminary results of in vitro susceptibility testing with the echinocandins suggest that some isolates of *C. parapsilosis* exhibit higher MICs than do other *Candida* species [17]. Although the clinical consequences of these findings are not known, the recent report of the development of multiple-echinocandin resistance during exposure to these agents is a concern [18], especially because these agents have been increasingly used as primary therapy for candidemia.

Candida rugosa has been rarely reported as a human pathogen. In 1994, an outbreak of fungemia due to this organism was reported in a burn unit in the United States [19]. No obvious source was identified, and the authors associated its occurrence with the use of topical nystatin in burn wounds [19]. More recently, another outbreak was reported in an intensive care unit of a tertiary care hospital in Brazil during a surveillance study of candidemia in 6 institutions from 3 different cities. Six cases were identified within a 4-month period. All patients had coexisting exposures that were very usual for patients with candidemia, such as the presence of a central venous catheter, antibiotic therapy, surgery, and mechanical ventilation. Again, no source of the infections was identified, but DNA typing showed that all isolates were genotypically related [20]. In a subsequent study performed in the same unit, 349 patients were prospectively evaluated with biweekly cultures of samples from sites of colonization to investigate the predictive value of *Candida* colonization in the diagnosis of candidemia [21]. Surprisingly, 15% of the 1400 cultures with positive results grew *C. rugosa,* which accounted for 43.7% of the 32 episodes of candidemia (data not shown). Therefore, although most reports of infection due to *C. rugosa* occurred in the context of outbreaks, there are data suggesting that this species may be endemic to some institutions.

Trichosporon species have been associated with fungemia and disseminated infection since the late 1980s. This organism most frequently causes disseminated infection in neutropenic patients with cancer [22]. By contrast, in a recent report from a single cancer center, most infections were catheter-related fungemias [2]. The reasons for these changes are not clear, but it is possible that the widespread use of fluconazole may have played some role, because this agent is active in vitro against *Trichosporon* species [23]. More recently, trichosporonosis has been reported in neonates [24]. Most patients were born prematurely, with a mean birth-weight <1000 g. The majority of cases were of disseminated infection, and, in >90% of cases, the fungus was isolated from the respiratory tract.

OTHER EMERGING YEASTS

Cryptococcal infections occur with a near worldwide distribution in immunosuppressed hosts. Infections typically are caused by *Cryptococcus neoformans;* however, *Cryptococcus gattii* causes disease in immunocompetent people in a geographically restricted fashion, with most cases occurring in Australia. A notable recent development is the recognition of *C. gattii* as a cause of invasive infection in animals and immunocompetent people on Vancouver Island, Western Canada [25, 26]. An outbreak that now involves >100 people has been occurring since 1999 [25] (K. Bartlett, personal communication). The organism, which is thought to thrive only in tropical regions, was recovered in the environment in a temperate climatic zone. Precisely why the organism emerged in this region has not been determined; it has been postulated that environmental factors—namely, a regional warming trend—may support its environmental propagation [26]. More studies are warranted to determine the clinical significance of this fungus and to define how the environmental factors may play a role in supporting the emergence of pathogenic fungi.

EMERGING MOLDS

The epidemiology of mold infections has changed substantially in the past 10 years. The incidence of invasive aspergillosis (IA) has increased significantly [27], and infections caused by molds that exhibit resistance to conventional antifungal agents, such as *Fusarium* species and the Zygomycetes, have been increasingly reported [28].

Most cases of IA occur in patients with hematologic malignancies or in transplant recipients (especially recipients of HSCTs, lung transplants, and liver transplants). In the former group, acute myeloid leukemia is the most frequent underlying condition [29], but, in recent years, IA has been increasingly diagnosed in patients with multiple myeloma. In a study of recipients of HSCTs, the risk of IA was 4.5 times greater in patients with multiple myeloma, compared with the risk for patients with chronic myeloid leukemia in the chronic phase [3]. In an epidemiologic study of 15 health care centers, 31 cases of IA in patients with multiple myeloma were identified in a 12-year period. Of these cases, 74% were diagnosed in the last 5 years of the study [30]. Remarkably, neutropenia was present in only 51% of patients with IA and myeloma, and all nonneutropenic patients had received high doses of corticosteroids. In a study of 69 autopsies performed on patients with multiple myeloma, IA had been diagnosed in 53% of the 38 deaths associated with infection, and IA was identified by autopsy in 45% of recipients of allogeneic HSCT, 21% of recipients of autologous HSCT, and 25% of patients who had completed a course of chemotherapy [31]. The increased number of reports of IA in patients with multiple myeloma may be related to changes in its treatment, with the incorporation of the concept of sequential aggressive therapy into the practice of intensive chemotherapy, double autologous transplantation, and nonmyeloablative allogeneic transplantation [32].

The time of onset of IA in recipients of allogeneic stem-cell engraftment has changed. Now, the infection typically occurs late, after HSCT is complete, when recipients are receiving immunosuppressive drugs (especially high doses of corticosteroids) for the treatment of graft-versus-host disease [3]. This shift is likely caused by changes in transplant procedures that have resulted in a reduction in the duration of neutropenia and an increase in the incidence and severity of graft-versus-host disease. Examples of changes in transplantation procedures include the use of peripheral blood instead of bone marrow as the source of stem cells, transplantation with reduced-intensity conditioning regimens (e.g., nonmyeloablative transplant), mismatched and unrelated transplant donors, donor lymphocyte infusion, and the use of monoclonal antibodies, such as infliximab [33] and alemtuzumab [34].

Late onset of IA has also been reported to have occurred in liver transplant recipients for a number of reasons, including a better survival of the organism in the early posttransplantation period, late occurrence of cytomegalovirus disease, and a higher number of patients with late allograft dysfunction [35].

Another trend of IA is the increasing number of reports of infections caused by species other than *Aspergillus fumigatus*. Of particular concern is *Aspergillus terreus,* because of its in vitro resistance and poor clinical response to amphotericin B [23]. In a single-center study, *A. terreus* accounted for 2.1% of cases of IA in 1996 and 10.2% of cases in 2001 [36]. The reasons why the relative incidence of infection due to *A. terreus* is increasing are not clear. The prognosis of IA caused by *A. terreus* is poor, with an overall mortality rate of 66%, and patients treated with voriconazole seem to have a better outcome [37]. Finally, infections caused by a recently recognized species of *Aspergillus* have been reported [38, 39]. The organism, which, according to classical morphological typing methods, is typically identified as *A. fumigatus,* clusters as a unique species with multilocus sequence typing [39], supporting the proposed designation of "*Aspergillus lentulus.*" Representative isolates have now been identified in multiple US health care centers and in Australia; the organism may be of particular interest because isolates exhibit low susceptibility to multiple antifungals in vitro. The clinical significance of this organism is a topic of current study.

Zygomycosis has emerged as a significant infection in transplant recipients. In a multicenter survey of fungal infections in transplant recipients, the proportion of cases of zygomycosis increased from 4% to 25% between 2001 and 2003. Among HSCT recipients, there were 4 cases of zygomycosis among recipients of 4358 transplants (0.09% of recipients) between March 2001 and April 2002, compared with 11 cases in recipients of 6660

transplants (0.17% of recipients) between May 2002 and June 2003 [40]. Multivariate analysis of risk factors associated with zygomycosis, compared with those associated with IA, revealed that the previous exposure to voriconazole was significant for both HSCT (OR, 7.7) and solid-organ transplantation (OR, 10.7). The association between the use of voriconazole and zygomycosis is further supported by 4 reports of cases of breakthrough zygomycosis in 15 patients receiving voriconazole therapy [14, 41–43], as well as a single-center case-control study that identified the previous exposure to voriconazole as a significant risk factor for zygomycosis by multivariate analysis [44]. Although the use of voriconazole may have contributed to the occurrence of zygomycosis, other factors may be equally important. As pointed out by Kauffman [4], there are some data indicating that the incidence of zygomycosis was increasing before the introduction of voriconazole in clinical practice. Other factors likely associated with the recent increase include the severity and type of immunosuppression. In one recent report, all patients who developed zygomycosis after neutrophil engraftment had severe graft-versus-host disease and had previously received high doses of corticosteroids and/or antithymocyte globulin. Another explanation for the increase in the incidence of zygomycosis is the potential decrease in IA-related mortality in most recent years. It is possible that the control of a highly aggressive infection has allowed patients to live long enough to develop a subsequent infection with persistent immunosuppression. With this in mind, zygomycosis may be considered the "third threat" for fungal infections in recipients of allogeneic HSCTs, after infections caused by *C. albicans* and *A. fumigatus,* each of which are more likely to occur in patients who are not receiving an effective preventative regimen.

There has been an increasing number of reports of fusariosis in immunocompromised patients. Data from a multicenter retrospective study of fusariosis in HSCT recipients showed that the rate of infection has increased over time [5]. The main reason for this increase seems to be severe immunosuppression, because the incidence of fusariosis was higher in transplant recipients with mismatched donors and because most patients had either severe neutropenia or graft-versus-host disease. Indeed, a significant number of cases were diagnosed very late after transplantation (>1 year) and none of these patients was neutropenic. This population of patients could be at risk for fusariosis because of severe T cell–mediated immunodeficiency.

In addition to these infections, a broad list of other fungi, including *Scedosporium* species, *Acremonium* species, and *Phialemonium* species, has been occasionally reported as causes of infection in immunocompromised patients. An increase in the incidence of non-*Aspergillus* mold infections has been observed in recipients of liver transplants [45] and HSCTs [27]. This increase in incidence is likely a reflection of more severe immunosuppression. Of interest is that many of these organisms appear to exhibit some geographical restriction; for instance, *Fusarium* infections have been reported more frequently in medical centers in the southern United States and South America [5], and *Scedosporium* infections occur more frequently in Spain [46]. Whether this reflects reporting bias, the distribution of hosts at risk, or an environmental influence on fungal prevalence will need to be further elucidated.

CONCLUSIONS

Fungi have been recognized as a cause of serious infection with increased frequency during the past 2 decades. This increase likely reflects multiple factors, including changes in hosts at risk and improvements in diagnostic methods. In more recent years, multiple organisms have emerged as new concerns. The discovery of "new" species and the widening of geographic distributions of previously recognized organisms emphasizes that our understanding of fungal epidemiology is critically dependent on global collaborative efforts. The appearance of organisms with variable susceptibilities to antifungal drugs emphasizes the clinical importance of establishing microbial diagnoses. Changes in hosts susceptible to infection, practice patterns, and diagnostic methods, and possibly changes in climatic influences, will likely continue to alter the epidemiology for years to come.

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