CURRENT OPINION

Drugs 2007; 67 (13): 1803-1812
0012-6667/07/0013-1803/$49.95/0



# Changing Epidemiology of Rare Mould Infections

## Implications for Therapy

*Anurag N. Malani* and *Carol A. Kauffman*

Division of Infectious Diseases, University of Michigan Health System, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan, USA

## Abstract

There has been an increase in rare mould infections in recent decades. These infections have been reported primarily in severely immunocompromised patients. The emergence of these organisms is multifactorial and can be related to more intense immunosuppression, the prolonged survival of patients who have what were previously fatal diseases, and the selective pressure of broad spectrum antifungal agents used for prophylaxis or therapy. Among these rare mould infections, the Zygomycetes are the most commonly encountered, and in some institutions the increase in these organisms appears to be associated with the use of voriconazole. *Aspergillus terreus*, a species that is resistant to amphotericin B, and less frequently, *A. ustus* and *A. lentulus*, have been noted increasingly as causes of invasive aspergillosis in tertiary care centres in the US. Several species of *Scedosporium* with innate resistance to many antifungal agents have emerged as major causes of disseminated mould infections that are frequently very difficult to treat. Among patients who have haematological malignancies, are neutropenic or have received a haematopoietic stem cell transplant, infections due to *Fusarium* species respond poorly to many antifungal agents. Dematiaceous, or brown-black, fungi, most often associated with chronic localised infections, are now increasingly reported as a cause of disseminated infection in immunosuppressed hosts.

Concomitant with the increased number of infections with these rare moulds, several new mould-active antifungal agents have been developed. The new expanded spectrum azole, voriconazole, has changed our approach to moulds such as *S. apiospermum, Fusarium* species and *A. terreus* that are amphotericin B resistant. Posaconazole, the most recently approved expanded spectrum azole, is the first drug in the azole class to show activity against the Zygomycetes and has proven extremely useful for step-down therapy after initial treatment with amphotericin B. It is not known whether posaconazole is effective as primary therapy for zygomycosis; the use of this agent for that purpose awaits clinical trials with the recently developed intravenous formulation of posaconazole.

Over recent decades, there have been increasing reports of infections due to what used to be thought of as exotic moulds.[1-4] The reasons for the increase in rare mould infections are primarily related to the increasing numbers of patients who have received haematopoietic stem cell or solid organ transplants, have haematological malignancies, or are treated with immunosuppressive regimens for a variety of different diseases. Just as important as the increasing numbers of transplants performed worldwide,

are the increasingly immunosuppressive regimens used to ensure the success of the transplanted organs and to combat graft-versus-host disease (GVHD). For example, protocols used routinely in the last few years have decreased the time to engraftment for haematopoietic stem cell transplantation but have increased the risk for GVHD,[5] and GVHD is increasingly treated with intense immunosuppression, including high dose corticosteroids and tumour necrosis factor (TNF) antagonists, increasing the risk for life-threatening mould infections.[6,7] Not surprisingly, reports of rare mould infections tend to be primarily from tertiary care and cancer centres.

Some mould infections occur predominantly in certain geographic regions,[8] while others are increasing worldwide.[9,10] Outbreaks of mould infections traced back to contaminated materials or a point-source in the environment occur periodically,[11,12] and the use of certain antifungal agents or other drugs has been associated with the emergence of more resistant mould infections.[13]

This article reviews the epidemiology of the most commonly seen of these rare mould infections and their treatment, and the role of the new triazoles, voriconazole and posaconazole, is emphasised.[14,15] These agents have revolutionised our approach to these rare infections and have both increased survival rates and allowed safer, better tolerated treatment regimens to be used in very ill patients.

## 1. Zygomycosis

The Zygomycetes are a class of moulds that are found worldwide in soil, decaying organic matter and contaminated foods. Within this class, the order Mucorales constitutes most human pathogens, including the genera *Rhizopus, Mucor* and *Rhizomucor*. *Rhizopus oryzae* is the species most commonly isolated. These fungi are opportunistic pathogens, causing disease almost entirely in immunosuppressed patients.[9] The major mode of transmission for development of human infection is inhalation of spores, but cutaneous inoculation and ingestion of contaminated foods can also lead to infection.

### 1.1 Epidemiological Trends

Several aspects of the epidemiology of infection with the Zygomycetes have changed in recent years (table I). In a review of 929 cases of zygomycosis since 1940, the most common underlying risk factors were diabetes mellitus (36%), haematological malignancy (17%), and bone marrow or solid organ transplantation (12%); deferoxamine chelation therapy, injection drug use and trauma were less common risk factors.[10] Diabetes remains the most common risk factor, but in the past 2 decades there has been a dramatic increase in zygomycosis in patients who have haematological malignancies or who have received a haematopoietic stem cell or solid organ transplant.[10] This increase is most likely to be as a result of the increased numbers of patients undergoing transplantation and being treated with aggressive chemotherapy.[4,16]

In addition to the above noted increase in cases of zygomycosis, at least seven medical centres that care for cancer and transplant patients in the US and Europe have reported an increase in cases of zygomycosis since 2004, especially in those patients who had received voriconazole for prophylaxis, empirical therapy or treatment.[17-23] A case-controlled study showed that prophylaxis with voriconazole was a significant risk factor for the development of zygomycosis (odds ratio = 10.37).[23] In most of

**Table I.** Emerging trends in the epidemiology of infection with the Zygomycetes

| Observation | Comment |
|---|---|
| Increasing proportion in transplants and patients with haematological cancers, and decreasing proportion in patients with diabetes mellitus | Increased numbers of transplants performed and increasingly aggressive treatment of haematological cancers has led to these changes |
| Decreasing incidence in patients receiving chelation therapy | Chelation therapy now rarely used in dialysis for iron or aluminium overload states |
| Voriconazole appears as a new risk factor for zygomycosis | Noted mostly in HSCT patients with severe GVHD receiving voriconazole for prophylaxis |
| Increase in pulmonary infection and decrease in rhinocerebral infection | Related to decrease in proportion of patients with diabetes as risk factor |

**GVHD** = graft-versus-host disease; **HSCT** = haematopoietic stem cell transplant.

these reports, a majority of cases occurred late after haematopoietic stem cell transplantation and in the presence of severe GVHD that was treated with high dose corticosteroids and other aggressive immunosuppressive therapy, such as anti-thymocyte globulin and TNF antagonists. The relationship of this increase in zygomycosis to the use of voriconazole is striking[13] and is likely to be related to the effectiveness of voriconazole against most moulds, with the exception of the Zygomycetes, against which it has no activity.[24] Several cases of zygomycosis have been reported in patients who were receiving an echinocandin for treatment or prophylaxis,[23,25] but this association was shown to be not significant.[23] It is also plausible that the increasingly immunosuppressive regimens now used for GVHD have also contributed to the increasing rates of zygomycosis.

Another trend noted in recent years is the increase in cases of pulmonary and disseminated zygomycosis, whereas classically these organisms caused invasive rhinocerebral infection.[10] This trend appears to be directly related to the increase in zygomycosis among patients who have haematological malignancies and/or have undergone transplantation. Rhinocerebral involvement still remains the most common manifestation in patients who have diabetes.

The number of cases of zygomycosis related to the use of the iron chelator deferoxamine peaked in the 1980s when this agent was used for both iron and aluminium overload states, predominantly in haemodialysis patients.[26,27] Changes in the dialysis process that have eliminated aluminium excess and the routine use of erythropoietin have led to the virtual disappearance of zygomycosis in the dialysis population. Patients with myelodysplastic syndrome and other haematological diseases who require deferoxamine therapy for iron overload remain at risk for zygomycosis.

### 1.2 Treatment

Since amphotericin B deoxycholate was introduced for widespread use in the 1960s, mortality in patients who have zygomycosis, including those with localised cutaneous involvement, has remained essentially unchanged, with overall mortality rates of ≈47–57%, and mortality rates approaching 100% in those patients who have disseminated infection.[10]

Treatment of zygomycosis requires a multifaceted strategy. Eliminating or reducing the metabolic or immunosuppressive factors that predisposed the patient to the infection is foremost. Surgical debridement is essential for removal of necrotic tissue so that antifungal therapy can be effective in inhibiting growth of the organism in the remaining viable tissues. This combined approach is most successful in diabetic patients who have rhinocerebral infection and in whom hyperglycaemia and acidosis can be corrected quickly. On the other hand, it is extremely difficult to resect pulmonary lesions in a patient who has a haematological malignancy and whose thrombocytopenia and neutropenia cannot be corrected.

Amphotericin B has been the standard of therapy for the treatment of zygomycosis since its introduction. In the last decade, lipid formulations of amphotericin B rather than amphotericin B deoxycholate have been increasingly used in order to both increase the amount given daily and decrease nephrotoxicity.[28] A retrospective comparison of outcomes noted a 69% survival for patients who received a lipid formulation of amphotericin B compared with a 61% survival rate for patients who were treated with amphotericin B deoxycholate.[10] Review of the CLEAR (Collaborative Exchange of Antifungal Research) database showed a 52% response rate for recipients of amphotericin B lipid complex (ABLC).[29]

Posaconazole, an extended-spectrum, oral triazole that was recently approved in Europe and the US, has significant *in vivo* and *in vitro* activity against the Zygomycetes.[24] The clinical data have come entirely from salvage trials in patients who either were intolerant of or in whom therapy with conventional agents failed (mostly lipid formulations of amphotericin B).[30-32] The largest of these studies included 91 patients who had probable or proven zygomycosis. Overall success (complete and partial response) at 12 weeks following posaconazole treatment was 60%; only 13 (14%) had complete resolution and 42 (46%) had a partial response.[32] These data are extremely promising. However, it must be remembered that some of these patients received combination therapy with an

amphotericin B formulation and posaconazole for at least a week, and all patients with prior treatment with amphotericin B would have had this agent remaining in tissues for weeks after posaconazole was started.

Posaconazole is a much-needed addition to the limited arsenal for zygomycosis.[16] However, a major drawback is that currently the only available formulation is an oral suspension that requires dose administration 2–4 times daily with fatty food or high fat supplements for effective absorption.[33] A total of 800mg daily is the maximum dosage; higher amounts do not lead to any increase in serum posaconazole concentrations.[34] An intravenous formulation of posaconazole is being developed and will possibly be available for clinical trials for initial therapy of zygomycosis in the next year.

Until an intravenous formulation of posaconazole is shown to be effective for the primary treatment of zygomycosis, lipid formulations of amphotericin B remain the treatment of choice for these infections. After an initial response to amphotericin B, therapy can be changed to oral posaconazole for long-term therapy until the infection has cleared. Whether combination therapy with posaconazole and amphotericin B should be used is not known and it is unlikely that any clinical trials will be performed in the near future to investigate this.

A variety of adjunctive measures, including colony-stimulating factors, interferon-γ and hyperbaric oxygen, have been reported to increase survival, but experience is limited to a few cases and currently none of these measures can be recommended.[10,35-37] A novel approach, used successfully in one patient with *Rhizopus* infection, has been to use a new iron-chelating agent, deferasirox, in conjunction with an antifungal agent.[38] This chelator and several other new chelators, in contrast to deferoxamine, cannot be utilised by the fungus, but instead enhance killing of the organism.[28,39]

## 2. Aspergillosis

Aspergillosis remains the most important mould infection in immunosuppressed patients, as it has during recent decades. Aspergillosis will be discussed only in the context of new species that have emerged in the last decade. *Aspergillus terreus* and, less frequently, *A. ustus* and *A. lentulus*, have been reported increasingly as causes of invasive aspergillosis.[1,40-52]

### 2.1 Epidemiological Trends

A review of 1477 *Aspergillus* isolates from 24 medical centres from 1995 noted that *A. terreus* was the fourth most common *Aspergillus* species, but it comprised only 3% of isolates.[40] However, isolation of *A. terreus* was more often associated with invasive disease than isolation of *A. fumigatus*, and most reports of *A. terreus* infections have come from cancer centres and tertiary care centres that care for immunosuppressed hosts.[41-44] *A. terreus* isolates rose from 1.5% of all *Aspergillus* isolates in 1996 to 15.4% of all isolates in 2001 at the University of Alabama.[41] Of 83 cases of invasive fungal infection included in a multicentre, retrospective review, 65% had a haematological malignancy and 45% had undergone a haematopoietic stem cell transplant.[42] *A. ustus* and *A. lentulus* have been described almost entirely in recipients of stem cell transplants.[50-52]

*A. terreus* infections have been reported from around the globe, but the organism appears to be more prevalent in warmer climates. The presumed source for exposure of most patients is soil. A hospital-associated outbreak has been described in which the soil taken from potted plants placed near the haematology ward was linked by molecular typing methods to four of nine *A. terreus* infections in patients with leukaemia.[49] *A. terreus* has also been isolated from air samples and cultures from showerheads in hospitals.[44] The environmental niche for *A. ustus* and *A. lentulus* has not been defined.

### 2.2 Treatment

The importance of *A. terreus* is 2-fold: (i) it appears to be more consistently associated with invasive disease than other species of *Aspergillus*; and (ii) it is resistant to amphotericin B.[44,45] In an experimental rabbit model of *A. terreus* pulmonary infection, animals treated with amphotericin B did no better than animals receiving no therapy. Those animals treated with azoles (posaconazole and itraconazole were the two azoles studied) had fewer

**Table II.** Differences between *Scedosporium apiospermum* and *S. prolificans*

| Parameter | *S. apiospermum* | *S. prolificans* |
|---|---|---|
| Geographic distribution | Worldwide | Spain, Australia; less frequent in UK, US, South America |
| Environmental niche | Water, soil, manure | Soil, manure |
| Mycological aspects | Hyaline hyphae rarely sporulate *in vivo*; positive blood cultures rare; *Pseudallescheria boydii* is sexual form | Brown-black hyphae frequently sporulate *in vivo*; positive blood cultures common; sexual form not established |
| Clinical disease | Mycetoma, localised infections most common; allergic bronchopulmonary disease in cystic fibrosis; disseminated infection in immunosuppressed patients | Mycetoma, localised infections most common; disseminated infection in immunosuppressed patients |
| *In vitro* susceptibility to antifungal agents | Voriconazole and posaconazole most active; resistant to amphotericin B and echinocandins | Resistant to all agents |
| Treatment | Voriconazole or posaconazole | Voriconazole with terbinafine possibly effective |

organisms remaining in the lung and had improved survival.[45]

In humans, survival with *A. terreus* infection has been only ≈20–30%, but this can be ascribed to the use of amphotericin B therapy for most of the earlier cases.[42,44] A retrospective review noted survival of only 27% among those receiving amphotericin B compared with 64% in a small number of patients who had received voriconazole as initial therapy.[42] Limited experience with posaconazole for salvage therapy shows that it is also effective for *A. terreus* infections.[46] The echinocandins also have activity against *A. terreus*; experimental animal and clinical experience is almost entirely with caspofungin to date, but presumably the other echinocandins will be similar.[47,48] With the use of voriconazole as the preferred treatment for invasive aspergillosis, mortality rates for *A. terreus* should improve because the most active agent will be administered as initial therapy before the species of *Aspergillus* has been identified.

There is minimal experience treating *A. ustus* and *A. lentulus* infections; definitive treatment recommendations cannot be made. However, it has been shown that both species are often resistant to many antifungal agents.[50-52]

## 3. Scedosporium Infections

The genus *Scedosporium* contains two prominent pathogens, *Scedosporium apiospermum* and *S. prolificans*, which differ in their epidemiological niches, mycological characteristics and antifungal susceptibility profiles (table II).

### 3.1 Epidemiological Trends

*S. apiospermum*, the asexual phase of *Pseudallescheria boydii*, is found worldwide in temperate climates in tidal flats, swamps, ponds, manure and soil.[53,54] Because of the association with water, *S. apiospermum* has been reported as a cause of pneumonia and disseminated infection, including brain abscesses in near-drowning victims.[55,56] *S. prolificans* is found in soil predominantly in Spain and Australia, and has also been reported less often from the UK and the US.[8,57]

For years, *S. apiospermum* has been known to cause mycetoma, an indolent, disfiguring, non-life-threatening subcutaneous infection.[53] *S. prolificans* was first described in 1984 in patients with localised infections of bones and subcutaneous tissues.[58] The increase in cases of scedosporiosis in recent years is almost entirely manifest among immunosuppressed patients, including solid organ and haematopoietic stem cell transplant recipients, patients with haematological malignancies (especially acute leukaemia with neutropenia), and those receiving corticosteroids. Almost all of these cases are characterised by widespread dissemination, rather than localised infection.[8,12,53,54,59]

Another trend noted in recent years is the association of *S. apiospermum* with cystic fibrosis. In some patients, asymptomatic colonisation is the only manifestation, but in others, a picture indistinguishable from allergic bronchopulmonary aspergillosis occurs,[60] and combined infection with both *A. fumigatus* and *S. apiospermum* has been described.[61] It is not clear whether the frequency of reports of this

association is rising simply because of increased recognition of this organism or because there is indeed an increasing risk for exposure to *S. apiospermum* among patients with cystic fibrosis.

### 3.2 Treatment

Both species of *Scedosporium* are characterised by their resistance to amphotericin B and echinocandins, and in the case of *S. prolificans*, resistance to almost all available antifungal agents.[62-64] Itraconazole has modest activity against *S. apiospermum* and was used prior to the introduction of the second-generation triazoles, but is not currently recommended. *In vitro* studies show voriconazole to have the greatest activity against *S. apiospermum*, followed by posaconazole.[62,63] Although the number of patients remains small, it appears that voriconazole should be the agent of choice for *S. apiospermum* and that posaconazole could also be used for this infection.[12,64-66]

Voriconazole is also the most active agent against *S. prolificans*, but not at a level that would be beneficial *in vivo* for most patients. In one study, the voriconazole 90% minimum inhibitory concentration ($MIC_{90}$) was 4 μg/mL for *S. prolificans* compared with 0.25 μg/mL for *S. apiospermum*.[62] Because of the almost total resistance of *S. prolificans*, the addition of other agents to gain synergistic killing has been attempted. *In vitro* data show benefit when terbinafine, to which the organism is innately resistant, is added to voriconazole.[64] Although there are few data showing this to be effective clinically, there is little harm and the possibility of benefit makes this worthwhile to try.[67]

Mortality rates have been reported to be as high as 65–75% for *S. apiospermum* and 85–100% for *S. prolificans*.[8,12,53,54,57] However, with the availability of voriconazole and posaconazole, it is hoped that the mortality rates for *S. apiospermum*, if not for *S. prolificans*, will improve. A trend toward better outcomes was reported in transplant recipients who received voriconazole compared with those who received amphotericin B, but the numbers were small and the outcomes were not statistically significantly better.[59]

## 4. Fusarium Infections

Many species in the genus *Fusarium* are economically important plant pathogens and have been associated with localised infections and intoxications in humans for decades.[68] The most common human pathogens are *Fusarium solani*, which accounts for ≈50% of isolates, *F. oxysporum* and *F. moniliforme*.

### 4.1 Epidemiological Trends

*Fusarium* species are very common in the soil and on plants and decaying matter; they can cause human disease after inhalation, ingestion or direct inoculation. In the last 2 decades, there have been increasing reports of disseminated infection among highly immunosuppressed patients.[69-73] Most of these reports came initially from a few medical centres in the southern US,[70,72] but cases have been increasingly reported from tertiary care centres throughout the US, Europe and Brazil.[3,4,69,71,73,74] More than 90% of reported cases have occurred in patients who had a haematological malignancy and who were neutropenic,[69] but infection also occurs in haematopoietic stem cell and solid organ transplant recipients.[74]

Whether the hospital environment is a source for invasive *Fusarium* infections is debated. Some investigators in the southern US have found the highest concentrations of *Fusarium* species in the outside air during humid months and feel that acquisition is primarily outside of the hospital.[75] Other investigators in similar locations have implicated the hospital water supply,[76] but firm linkage of a colonised water supply to disease in patients remains unproven.

A recent outbreak of *Fusarium* keratitis among soft contact lens wearers was traced back to a particular brand of contact lens solution, which has been removed from the market.[11] The solution itself was not intrinsically contaminated, but contact lens cases of wearers who used this solution became contaminated with *Fusarium*, presumably from the environment or the wearer's hands, and then the mould was able to persist on the lens and invade the cornea causing sight-threatening disease.

## 5. Treatment

*Fusarium* species, especially *F. solani*, are resistant to many antifungal agents.[77-79] Amphotericin B has been recommended most often, but *in vitro* activity is low and clinical responses have been discouraging.[70,71] Higher dosages of amphotericin B, which can be achieved using a lipid formulation, have been reported to have better outcomes than amphotericin B deoxycholate.[29,80] Both voriconazole and posaconazole have better *in vitro* activity than amphotericin B against many species of *Fusarium*.[77] Clinical responses have been encouraging with both of these new triazoles,[15,65,81] and they have assumed a role in primary therapy of fusariosis. Salvage therapy with voriconazole was associated with a 45% complete or partial response rate after failure or intolerance of prior therapy.[65] In 21 cases, which is the largest series reported thus far, salvage therapy with posaconazole was associated with a 48% complete or partial response rate after failure or intolerance of prior therapy.[81] Echinocandins have no activity against *Fusarium* species and should not be used.[79] Most importantly, if neutropenia does not resolve, the mortality rate approaches 100% no matter what antifungal agent is used.[69,71,73]

## 6. Other Hyaline and Pigmented Moulds

The organisms discussed in the previous sections are the most common of the rare moulds that are human pathogens, but many others have been reported with increasing frequency in immunosuppressed patients.[2,3,82-87] Some of these have clear hyphae, similar to the hyphae of *Aspergillus* and are called hyaline moulds; examples include *Acremonium*, *Paecilomyces* and *Trichoderma*.[84-86] Others contain melanin and are termed dematiaceous moulds or phaeohyphomycoses, and many, such as *Curvularia* and *Bipolaris*, commonly cause allergic upper respiratory disease in healthy hosts. However, these – as well as *Alternaria, Exophiala, Ochroconis* and others – can cause brain abscess, pneumonia and disseminated infection in immunosuppressed hosts.[82,83,87]

### 6.1 Epidemiological Trends

Almost all of these moulds live in the environment, and patients acquire infection during the course of everyday living through the lungs, upper airways or by traumatic inoculation. Patients who have received transplants or corticosteroids, or who are neutropenic with an underlying haematological malignancy, are at greatest risk for disseminated infection with these moulds. In a large review of 72 cases of disseminated phaeohyphomycosis, the overall mortality was 79%, but was even higher in the highest risk groups: 84% in those who were immunosuppressed and 100% in those who remained neutropenic.[82] However, most of these cases were reported prior to the availability of the new azoles.

### 6.2 Treatment

Many of these rare moulds are resistant to amphotericin B, but some appear susceptible to azoles.[88] Itraconazole has been reported to be effective therapy for many of the dematiaceous moulds.[89] This agent has been supplanted by voriconazole in most immunosuppressed hosts with invasive dematiaceous mould infection, although only minimal data are available regarding its benefit.[14,65] Posaconazole has also been used in a small number of patients and appears to be effective for some of these infections.[15,66] Whether voriconazole and posaconazole will assume larger roles in the treatment of these rare infections remains to be determined, but preliminary results are encouraging. For most of these cases, *in vitro* susceptibility studies should be performed at a reference laboratory and treatment individualised using these results and the clinical response to therapy.

## 7. Conclusions

The emergence of new mould infections is obviously multifactorial. Playing a major role are the types of immunosuppressive therapy now given for a variety of diseases and the length of time that patients remain alive with previously fatal diseases. The selective pressure of very broad spectrum antifungal agents that are used for prophylaxis or long-term therapy is important for the emergence of some mould infections. Thus, voriconazole prophylaxis

appears to have played a major role in selecting for an increase in Zygomycete infections. As posaconazole use becomes routine for prophylaxis in patients with GVHD[90] and in leukaemic patients with prolonged neutropenia,[91] one wonders whether yet another 'new' emerging mould infection resistant to this broad-spectrum azole will begin to be seen in these high-risk patients. There will likely be no end to 'new' opportunistic moulds, but the new azole agents have afforded clinicians some degree of success in treating these infections.

## Acknowledgements

No funding was provided for preparation of this manuscript. Dr Malani has no conflicts of interest to report. Dr Kauffman has received grant funding from Merck, Astellas, and Schering-Plough, and is on the Speaker's Bureau for Merck, Astellas, Pfizer and Schering-Plough.

## References

1. Nucci M, Marr KA. Emerging fungal diseases. Clin Infect Dis 2005; 41: 521-6
2. Walsh TJ, Groll A, Hiemenz J, et al. Infections due to emerging and uncommon medically important fungal pathogens. Clin Microbiol Infect 2004; 10 Suppl. 1: 48-66
3. Husain S, Alexander BD, Munoz P, et al. Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-Aspergillus mycelial fungi. Clin Infect Dis 2003; 37: 221-9
4. Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002; 34: 909-17
5. Copelan EA. Hematopoietic stem cell transplantation. New Engl J Med 2006; 354: 1813-26
6. Marty FM, Lee SJ, Fahey MM, et al. Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. Blood 2003; 102: 2768-76
7. Cordonnier C, Ribaud P, Herbrecht R, et al. Prognostic factors for death due to invasive aspergillosis after hematopoietic stem cell transplantation: a 1-year retrospective study of consecutive patients at French transplantation centers. Clin Infect Dis 2006; 42: 955-63
8. Berenguer J, Rodriquez-Tudela JL, Richard C, et al. Deep infections caused by *Scedosporium prolificans*: a report on 16 cases in Spain and a review of the literature. Medicine 1997; 76: 256-65
9. Chayakulkeeree M, Ghannoum MA, Perfect JR. Zygomycosis: the re-emerging fungal infection. Eur J Clin Microbiol Infect Dis 2006; 25: 215-29
10. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005; 41: 634-53
11. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. JAMA 2006; 296: 953-63
12. Panackal A, Marr KA. *Scedosporium/Pseudallescheria* infections. Sem Respir Crit Care Med 2004; 25: 171-81
13. Kauffman CA. Zygomycosis: reemergence of an old pathogen. Clin Infect Dis 2004; 39: 588-90
14. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis 2003; 36: 630-7
15. Torres HA, Hachem RY, Chemaly RF, et al. Posaconazole: a broad-spectrum triazole antifungal. Lancet Infect Dis 2005; 5: 775-85
16. Kontoyiannis DP, Wessel VC, Bodey GP, et al. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis 2000; 30: 851-6
17. Imhof A, Balajee SA, Fredricks DN, et al. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. Clin Infect Dis 2004; 39: 743-6
18. Kobayashi K, Kami M, Murashige N, et al. Breakthrough zygomycosis during voriconazole treatment for invasive aspergillosis. Haematologica 2004; 89: ECR42
19. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med 2004; 350: 950-2
20. Vigouroux S, Morin O, Moreau P, et al. Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematological disease: attention required. Clin Infect Dis 2005; 40: e35-7
21. Siwek GT, Dodgson KJ, de Magalhaes-Silverman M, et al. Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. Clin Infect Dis 2004; 39: 584-7
22. Oren I. Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia. Clin Infect Dis 2005; 40: 770-1
23. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 2005; 191: 1350-60
24. Sun QN, Fothergill AW, McCarthy DI, et al. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. Antimicrob Agents Chemother 2002; 46: 1581-2
25. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004; 39: 1407-16
26. Boelaert JR, van Roost GF, Verqauwe PL, et al. The role of desferrioxamine in dialysis-associated mucormycosis: report of three cases and review of the literature. Clin Nephrol 1988; 29: 261-6
27. Daly AL, Velazquez LA, Bradley SF, et al. Mucormycosis: association with deferoxamine therapy. Am J Med 1989; 87: 468-71
28. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005; 18: 556-69
29. Perfect JR. Treatment of non-Aspergillus moulds in immunocompromised patients, with amphotericin B lipid complex. Clin Infect Dis 2005; 40: S401-8
30. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother 2006; 50: 126-33
31. Tobon AM, Arango M, Fernandez D, et al. Mucormycosis (zygomycosis) in a heart-kidney transplant recipient: recovery after posaconazole therapy. Clin Infect Dis 2003; 36: 1488-91
32. van Burik JA, Hare RS, Solomon HF, et al. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis 2006; 42: e61-5
33. Sansone-Parsons A, Krishna G, Calzetta A, et al. Effect of a nutritional supplement on posaconazole pharmacokinetics fol-

 

lowing oral administration to healthy volunteers. Antimicrob Agents Chemother 2006; 50: 1881-3
34. Ullmann AJ, Cornely OA, Burchardt A, et al. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. Antimicrob Agents Chemother 2006; 50: 658-66
35. Ferguson BJ, Mitchell TG, Moon R, et al. Adjunctive hyperbaric oxygen for treatment of rhinocerebral mucormycosis. Rev Infect Dis 1988; 10: 551-9
36. Garcia-Diaz JB, Palau L, Pankey GA. Resolution of rhinocerebral zygomycosis associated with adjuvant administration of granulocyte-macrophage colony-stimulating factor. Clin Infect Dis 2001; 32: e145-50
37. Sahin B, Paydas S, Cosar E, et al. Role of granulocyte colony-stimulating factor in the treatment of mucormycosis. Eur J Clin Microbiol Infect Dis 1996; 15: 866-9
38. Reed C, Ibrahim A, Edwards Jr JE, et al. Deferasirox, an iron chelating agent, as salvage therapy for rhinocerebral mucormycosis. Antimicrob Agents Chemother 2006; 50: 3968-9
39. Ibrahim AS, Edwards Jr JE, Fu Y, et al. Deferiprone iron chelation as a novel therapy for experimental mucormycosis. J Antimicrob Chemother 2006; 58: 1070-3
40. Perfect JR, Cox GM, Lee JY, et al. The impact of culture isolation of Aspergillus species: a hospital-based survey of aspergillosis. Clin Infect Dis 2001; 33: 1824-33
41. Baddley JW, Pappas PG, Smith AC, et al. Epidemiology of *Aspergillus terreus* at a university hospital. J Clin Microbiol 2003; 41: 5525-9
42. Steinbach WJ, Benjamin DK, Kontoyiannia DP, et al. Infections due to *Aspergillus terreus*: a multicenter retrospective analysis of 83 cases. Clin Infect Dis 2004; 39: 192-8
43. Iwen PC, Rupp ME, Langnas AN, et al. Invasive pulmonary aspergillosis due to *Aspergillus terreus*: 12-year experience and review of the literature. Clin Infect Dis 1998; 26: 1092-7
44. Steinbach WJ, Perfect JR, Schell WA, et al. In vitro analyses, animal models, and 60 clinical cases of invasive *Aspergillus terreus* infection. Antimicrob Agents Chemother 2004; 48: 3217-25
45. Walsh TJ, Petraitis V, Petraitiene R, et al. Experimental pulmonary aspergillosis due to *Aspergillus terreus*: pathogenesis and treatment of an emerging fungal pathogen resistant to amphotericin B. J Infect Dis 2003; 188: 305-19
46. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007; 44: 2-12
47. Barchiesi F, Spreghini E, Santinelli A, et al. Efficacy of caspofungin against *Aspergillus terreus*. Antimicrob Agents Chemother 2005; 49: 5133-5
48. Cooke FJ, Terpos E, Boyle J, et al. Disseminated *Aspergillus terreus* infection arising from cutaneous inoculation treated with caspofungin. Clin Microbiol Infect 2003; 9: 1238-41
49. Lass-Florl C, Rath P, Niederwieser D, et al. *Aspergillus terreus* infections in haematological malignancies: molecular epidemiology suggests association with in-hospital plants. J Hosp Infect 2000; 46: 31-5
50. Panackal AA, Imhof A, Hanley EW, et al. *Aspergillus ustus* infections among transplant recipients. Emerg Infect Dis 2006; 12: 403-8
51. Pavie J, Lacroix C, Hermoso DG, et al. Breakthrough disseminated *Aspergillus ustus* infection in allogeneic hematopoietic stem cell transplant recipients receiving voriconazole or caspofungin prophylaxis. J Clin Microbiol 2005; 43: 4902-4
52. Balajee SA, Weaver M, Imhof A, et al. *Aspergillus fumigatus* variant with decreased susceptibility to multiple antifungals. Antimicrob Agents Chemother 2004; 48: 1197-203
53. Guarro J, Kantarcioglu AS, Horre R, et al. *Scedosporium apiospermium*: changing clinical spectrum of a therapy-refractory opportunist. Med Mycol 2006; 44: 295-327
54. Castiglioni B, Sutton DA, Rinaldi MG, et al. *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*) infection in solid organ transplant recipients in a tertiary medical center and review of the literature. Medicine 2002; 81: 333-48
55. Dworzack DL, Clark RB, Borkowski Jr WJ, et al. *Pseudallescheria boydii* brain abscess: association with near-drowning and efficacy of high-dose, prolonged miconazole therapy in patients with multiple abscesses. Medicine (Baltimore) 1989; 68: 218-24
56. Bartczak JC, Steele RW, Lopez AA, et al. A near-drowning victim with pneumonia and hemiparesis. Infect Med 2002; 19: 98-103
57. Gosbell IB, Morris ML, Gallo JH, et al. Clinical, pathologic, and epidemiologic features of infection with *Scedosporium prolificans*: four cases and review. Clin Microbiol Infect 1999; 5: 672-86
58. Malloch D, Salkin IF. A new species of *Scedosporium* associated with osteomyelitis in humans. Mycotaxon 1984; 21: 247-55
59. Husain S, Munoz P, Forrest G, et al. Infections due to *Scedosporium apiospermum* and *Scedosporium prolificans* in transplant recipients: clinical characteristics and impact of antifungal therapy on outcome. Clin Infect Dis 2005; 40: 89-99
60. Cimon B, Carrere J, Vinatier JF, et al. Clinical significance of *Scedosporium apiospermum* in patients with cystic fibrosis. Eur J Clin Microbiol Infect Dis 2000; 19: 53-6
61. Lake FR, Tribe AE, McAleer R, et al. Mixed allergic bronchopulmonary fungal disease due to *Pseudallescheria boydii* and *Aspergillus*. Thorax 1990; 45: 489-91
62. Meletiadis J, Meis JFGM, Mouton JW, et al. In vitro activities of new and conventional antifungal agents against clinical *Scedosporium* isolates. Antimicrob Agents Chemother 2002; 46: 62-8
63. Gilgado F, Serena C, Cano J, et al. Antifungal susceptibilities of the species of the *Pseudallescheria boydii* complex. Antimicrob Agents Chemother 2006; 50: 4211-3
64. Meletiadis J, Mouton JW, Meis JFGM, et al. In vitro drug interaction modeling of combinations of azoles with terbinafine against clinical *Scedosporium prolificans* isolates. Antimicrob Agents Chemother 2003; 47: 106-17
65. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 2003; 36: 1122-31
66. Raad II, Graybill JR, Bustamante AB, et al. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. Clin Infect Dis 2006; 42: 1726-34
67. Howden BP, Slavin MA, Schwarer AP, et al. Successful control of disseminated *Scedosporium prolificans* infection with a combination of voriconazole and terbinafine. Eur J Clin Microbiol Infect Dis 2003; 22: 111-3
68. Nelson PE, Dignani MC, Anaissie EJ. Taxonomy, biology, and clinical aspects of *Fusarium* species. Clin Microbiol Rev 1994; 7: 479-504
69. Lionakis MS, Kontoyiannis DP. *Fusarium* infections in critically ill patients. Semin Respir Crit Care Med 2004; 25: 159-69
70. Boutati EI, Anaissie EJ. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. Blood 1997; 90: 999-1008
71. Nucci M, Anaissie EJ, Queiroz-Telles F, et al. Outcome predictors of 84 patients with hematologic malignancies and *Fusarium* infection. Cancer 2003; 98: 315-9
72. Nucci M, Anaissie E. Cutaneous infection by *Fusarium* species in healthy and immunocompromised hosts: implications for diagnosis and management. Clin Infect Dis 2002; 35: 909-20

73. Nucci M, Marr KA, Queiroz-Telles F, et al. *Fusarium* infection in hematopoietic stem cell transplant recipients. Clin Infect Dis 2004; 38: 1237-42

74. Patel R, Paya CV. Infections in solid organ transplant recipients. Clin Microbiol Rev 1997; 10: 86-124

75. Raad I, Tarrand J, Hanna H, et al. Epidemiology, molecular mycology, and environmental sources of *Fusarium* infection in patients with cancer. Infect Control Hosp Epidemiol 2002; 23: 532-7

76. Anaissie EJ, Kuchar RT, Rex JH, et al. Fusariosis associated with pathogenic *Fusarium* species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. Clin Infect Dis 2001; 33: 1871-8

77. Paphitou NI, Ostrosky-Zeichner L, Paetznick VL, et al. In vitro activities of investigational triazoles against *Fusarium* species: effects of inoculum size and incubation time on broth microdilution susceptibility test results. Antimicrob Agents Chemother 2002; 46: 3298-300

78. Arikan S, Lozano-Chiu M, Paetznick V, et al. Microdilution susceptibility testing of amphotericin B, itraconazole, and voriconazole against clinical isolates of *Aspergillus* and *Fusarium* species. J Clin Microbiol 1999; 37: 3946-51

79. Pfaller MA, Marco F, Messer SA, et al. In vitro activity of two echinocandin derivatives, LY303366 and MK-0991, against clinical isolates of *Aspergillus*, *Fusarium*, *Rhizopus*, and other filamentous fungi. Diagn Microbiol Infect Dis 1998; 30: 251-5

80. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis 1998; 26: 1383-96

81. Raad II, Hachem RY, Herbrecht R, et al. Posaconazole in the treatment of invasive fusariosis in patients with underlying hematologic malignancy and other conditions. Clin Infect Dis 2006; 42: 1398-403

82. Revankar SG, Patterson JE, Sutton DA, et al. Disseminated phaeohyphomycosis: review of an emerging mycosis. Clin Infect Dis 2002; 34: 467-76

83. Singh N, Chang FY, Gayowski T, et al. Infections due to dematiaceous fungi in solid organ transplant recipients: case report and review. Clin Infect Dis 1997; 24: 369-74

84. Guarro J, Gams W, Pujol I, et al. *Acremonium* species: new emerging fungal opportunists. In vitro antifungal susceptibilities and review. Clin Infect Dis 1997; 25: 1222-9

85. Orth B, Frei R, Itin PH, et al. Outbreak of invasive mycosis caused by *Paecilomyce lilacinus* from a contaminated skin lotion. Ann Intern Med 1996; 125: 799-806

86. Richter S, Cormican MG, Pfaller MA, et al. Fatal disseminated *Trichoderma longibrachiatum* in adult bone marrow transplant patients: species identification and review of the literature. J Clin Microbiol 1999; 37: 1154-60

87. Revankar SG, Sutton DA, Rinaldi MG. Primary central nervous system phaeohyphomycosis: a review of 101 cases. Clin Infect Dis 2004; 38: 206-16

88. McGinnis MR, Pasarell L. In vitro testing of susceptibilities of filamentous ascomycetes to voriconazole, itraconazole, and amphotericin B, with consideration of phylogenetic implications. J Clin Microbiol 1998; 36: 2353-5

89. Sharkey PK, Graybill JR, Rinaldi MG, et al. Itraconazole treatment of phaeohyphomycosis. J Am Acad Dermatol 1990; 23: 577-86

90. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. New Engl J Med 2007; 356: 335-47

91. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs fluconazole or itraconazole for prophylaxis in patients with neutropenia. New Engl J Med 2007; 356: 348-59

Correspondence: Dr *Carol A. Kauffman*, Division of Infectious Diseases, Veterans Affairs Ann Arbor Healthcare System, 2215 Fuller Road, Ann Arbor, MI 48105, USA.
E-mail: ckauff@umich.edu