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Treatment of zygomycosis: current and new options

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Zygomycosis is a frequently lethal invasive infection in high-risk patients such as the immunocompromised [especially haematopoietic stem cell transplant (HSCT) recipients] and patients with type 2 diabetes mellitus. However, zygomycosis has also been reported in individuals without known risk factors. The causative fungi are members of the order Mucorales and individual species within this group require a high level of laboratory skill for their identification. These organisms are resistant to voriconazole and also to the echinocandins, and although zygomycosis is less commonly documented than invasive aspergillosis in leukaemic and HSCT patients, there are recent reports suggesting that it has increased in incidence since the introduction of voriconazole. Zygomycosis can present clinically as rhinocerebral, pulmonary or disseminated disease which progresses rapidly. The management of cases is based on early diagnosis, surgical debridement when possible and aggressive antifungal therapy. Based on clinical experience, but without the benefit of comparative studies, liposomal amphotericin B has become the therapeutic agent of choice. Posaconazole is a new orally administered triazole antifungal and the first member of this class to have comparable *in vitro* activity to amphotericin B against most zygomycetes. Studies of salvage therapy of zygomycosis with posaconazole have yielded promising results and there are additional case reports of successful outcomes using these and other antifungal drugs as combination therapy. Adjunctive approaches that are showing promise but with limited clinical experience are iron chelation and immunotherapy.

Keywords: haematopoietic stem cell transplant, diabetes mellitus, liposomal amphotericin B, posaconazole

Introduction

Zygomycosis and mucormycosis are terms often used interchangeably in the medical literature to describe a group of frequently lethal mould infections that have a predilection for diabetic patients and also classically afflict steroid-treated or other severely immunocompromised individuals, such as haematopoietic stem cell transplant (HSCT) recipients. The zygomycetes belong to the order Mucorales.[1,2] The majority of human infections that they cause are due to fungi mostly belonging to the genera (principal species) *Rhizopus* (*R. arrhizus*), *Mucor* (*M. circinelloides*), *Rhizomucor* (*R. pusillus*), *Cunninghamella* (*C. bertholletiae*) and *Absidia* (*A. corymbifera*). Zygomycete infections are less frequent than invasive mycoses caused by *Aspergillus* spp. Incidence figures are difficult to collect as few national studies have been undertaken, but for the United States, the annual incidence of zygomycosis has been estimated as 1.7 infections per million population based on a study performed several years ago in three California counties in which the incidence of invasive aspergillosis (IA) was estimated to be 12.4 per million.[3]

Epidemiology and pathogenicity

Shared features of these organisms include thermotolerance and presence in environmental habitats such as soil and dust. The infectious propagules (spores) are inhaled and initially may establish an infection in the sinuses. Other, less common routes of acquisition include the intestinal tract following ingestion or by inoculation through breaches in or penetrating injuries to the skin.

These moulds can be widely recovered from the environment, yet the fact that zygomycosis is less common than IA suggests that they possess fewer virulence factors. The pathogenesis of zygomycete infections is less clearly understood than for aspergillosis and is largely based on animal model studies. Phagocytic cells play a critical role[4] but the ways in which their function is impaired specifically in patients with diabetes or on steroid therapy is not so clear.[1]

In immunocompetent hosts, it is known that the killing and removal of the Mucorales is mediated by both neutrophils and macrophages.[5] Macrophages kill intracellular spores by oxidative mechanisms, whereas neutrophils can damage fungal hyphae by extracellular mechanisms. Phagocytic cell-mediated inhibition of

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germination of spores is impaired by corticosteroids and diabetes. Therefore, deficiencies of circulating neutrophils (e.g. neutropenia) and impaired phagocyte function (as in diabetes mellitus or steroid therapy) are risk factors for this infection. Serum iron also plays a role in pathogenesis.[6] For example, in diabetic ketoacidosis, there is an increased availability of iron that facilitates fungal growth, while the iron chelator desferrioxamine can act as a siderophore to provide iron for fungal growth. Angioinvasion is a prominent feature of the infection progressing to tissue necrosis and infarction, and this presumably accounts for their ability to cause rapidly invasive infections sometimes with dissemination.

Clinical features

From a clinical standpoint, zygomycosis describes infections characterized by one or more of a triad of rhinocerebral, pulmonary and disseminated disease. Classic clinical features are facial swelling, with ocular involvement that often progresses to cerebral disease, either of which can be complicated by pulmonary or disseminated infection. Black necrotic lesions can also occur. However, the presentation of pulmonary zygomycosis often resembles that of IA in severely immunocompromised patients such as HSCT recipients. Comparison of the CT imaging features of zygomycosis and IA has shown that multiple (>10) lung nodules and pleural effusions are independent predictors of zygomycosis.[7] Diagnosis can be confirmed by biopsy of affected tissues, when accessible, where the presence of non-septate broad-based hyphal structures is seen. Cultures may prove negative. Genus/species identification is made on culturing the organism and documenting characteristic morphological features. Regrettably, the diagnosis is too often first made at autopsy.[8]

The moulds that cause entomophthoramycosis also belong to the class Zygomycetes and comprise *Conidiobolus* spp. and *Basidiobolus* spp. They principally cause nasal, facial and other subcutaneous infections, which may be persistent but rarely disseminate. These are rarely encountered outside of West Africa, India and Central and South America. Infected individuals, who usually exhibit normal immunity but may sometimes be immunocompromised, contract the pathogen from environmental sources such as soil.[2] However, due to their distinct nature, infections due to these organisms will not be considered further in this review.

Case series and reports describing zygomycosis, treatment approaches and outcomes

Roden *et al.*[9] reviewed 929 cases of zygomycosis that had been reported in the international literature up to 2004. In investigating risk factors, the largest group was patients with type 2 diabetes mellitus, followed by patients with no known risk factor, and thirdly patients with malignancy. Within the past three decades, the number of cases associated with malignancy, HSCT and intravenous drug abuse had increased as a proportion of the total. Rhinocerebral zygomycosis was more commonly associated with diabetes, whereas pulmonary infection occurred more often in those with malignancy. For treatment, various antifungal agents were used, with or without adjunctive therapies that included surgery, hyperbaric oxygen and granulocyte colony-stimulating factor. The survival rates reported for antifungal therapy alone ranged from 61% to 69% (amphotericin B, 61%; lipid formulations of amphotericin B, 69%; and an azole, 67%) compared with 70% for combined antifungal therapy and surgery. Multivariate analysis revealed that independent risk factors for increased mortality included disseminated infection, *Cunninghamella* spp. as the causative agent and renal failure. Antifungal therapy and surgery were independently associated with a decreased risk of mortality.

In a retrospective review of 15 patients with zygomycosis diagnosed at a non-oncology tertiary referral centre between 1999 and 2004,[10] the following observations were made: 9/16 episodes were associated with diabetes mellitus, whereas trauma, vascular disease, steroid therapy and neutropenia were the other, less commonly, documented contributory conditions. Ten episodes were due to *Rhizopus* spp. and six were due to *Mucor* spp. The most common sites of infection were wound, rhinocerebral, pulmonary and peritoneal. There was a 25% mortality rate. Liposomal amphotericin B was the most commonly used antifungal agent (10/15). Three cases who received itraconazole, voriconazole or amphotericin B were switched to liposomal amphotericin B. Twelve patients had surgical debridement in addition to antifungal therapy. Surgical intervention was associated with a trend towards reduced mortality but the numbers were too small to allow statistical significance to be reached. Three patients who additionally received hyperbaric oxygen therapy were among those who survived. Seven of 12 survivors were left with severe physical or other disabilities.

In a retrospective Italian study of 37 cases in patients being treated with chemotherapy for haematological malignancy,[11] most cases presented during neutropenia (89%). The median time between the onset of neutropenia and diagnosis was only 14 days; 61% of patients recovered from neutropenia a median of 7 days from diagnosis. Most had received oral azole or polyene antifungal prophylaxis and prior steroid therapy. A pulmonary focus of infection was most commonly documented *in vivo* (88%), followed by the CNS and sinus infection (each 17%). At autopsy (28 patients), the following organs showed the presence of infection: lungs (93%), CNS (35%), liver (10%), sinus (7%), eye (7%) and kidney (7%). Twenty-six of the patients received antifungal therapy, 22 of whom were treated with amphotericin B. Five had radical surgical debridement (two eye enucleation, two sinus debridement and one lobectomy). Treatment was successful in only nine patients and better outcome was associated with earlier diagnosis, localized infection and surgical debridement. During the course of a related study conducted in 1993, this infection accounted for 12% of all documented invasive mould infections in a multicentre study of 162 cases.[12]

Kontoyiannis *et al.*[13] performed a prospective study of 27 patients with zygomycosis who were attending a tertiary care cancer centre. They either had leukaemia and/or were undergoing bone marrow transplantation. Using multivariate analysis, the authors compared clinical and laboratory data from these cases with 54 cases of IA and with a further 54 matched patients who did not develop invasive fungal infection (IFI). Independent risk factors for zygomycosis were: prior exposure to voriconazole (P value $= 0.001$); diabetes ($P = 0.003$); and malnutrition ($P = 0.045$). Compared with cases of aspergillosis, prior voriconazole prophylaxis and sinusitis as an initial presentation favoured the diagnosis of zygomycosis. Time to diagnosis after allogeneic bone marrow transplant (BMT) was 43 days for zygomycosis and 93 days for aspergillosis. Mortality at 12 weeks following diagnosis was 54% in the zygomycosis group

versus 28% in patients without IFI. Comparing data between 2000 and 2003, they recorded a significant increase in incidence of zygomycosis, which they showed was temporally related to the increasing use of voriconazole over that period. The association between zygomycosis and prior voriconazole exposure has also been reported in a more recent study.[14]

Marr *et al.*[15] have also noticed an increase in incidence of zygomycosis among their BMT patients through the period 1985–99. There were 29 cases documented, most of whom presented >90 days post-transplant. Graft-versus-host disease was a significant risk factor. The median duration of survival was longer at 66 days than for patients with other invasive mould infections, including aspergillosis, although the overall 1 year survival in all groups was only 20%.

Susceptibility of zygomycetes to antifungal agents *in vitro* and implications for therapy

Almyroudis *et al.*[16] determined the MICs of currently available systemic antifungal agents, including the recently licensed triazole posaconazole, against their collection of 217 zygomycetes that had been referred from other hospitals. They used the CLSI method M38-A for susceptibility testing of filamentous fungi.[17] Eleven groups of isolates were tested of which the largest was *Rhizopus* spp. ($n = 101$). Overall, amphotericin B was the most active agent, followed by posaconazole. Itraconazole was less active than either of these drugs, whereas both fluconazole and voriconazole showed poor or no activity; similarly caspofungin and flucytosine showed little activity against the isolates tested. The majority of *Rhizopus* and *Mucor* spp. were considered to be highly susceptible to amphotericin B using a breakpoint of ≤1 mg/L, whereas the majority (range 64% to 100%) of isolates were susceptible to posaconazole using a breakpoint of ≤0.5 mg/L, an exception being the *M. circinelloides* group where all three isolates tested were resistant. It is interesting that *C. bertholletiae* was identified as the least susceptible species in the collection, which may explain in part the higher mortality that has been associated with this pathogen. The data appear to correlate with clinical and animal model experience showing that amphotericin B and posaconazole have greatest activity and *in vivo* efficacy, whereas fluconazole, voriconazole, flucytosine and the echinocandins have little or no efficacy and therefore no role as single agent therapy for zygomycosis. However, the authors of this study caution against over-interpretation of these data for management purposes since there are no studies available that confirm clinical outcome correlates with MIC. Sabatelli *et al.*[18] tested 86 zygomycetes using the triazoles and amphotericin B, also using the CLSI methodology, and obtained similar results. Comparable data have been published by Pfaller and Diekema[19] who additionally found that the investigational triazole ravuconazole had poorer activity than posaconazole.

The findings from a comparison of three MIC test methods for 45 zygomycetes resulted in the authors recommending the CLSI method over Etest or Sensititre YeastOne as the reference procedure for determining antifungal drug susceptibility.[20] Again, this study has confirmed the superior activity of amphotericin B and posaconazole over other antifungals.

The *in vitro* effects of the combination of posaconazole with caspofungin have been evaluated against 12 zygomycete strains using a chequerboard format with a modification of the CLSI method.[21] Even though all strains were highly resistant to caspofungin, the combination showed a synergistic interaction with fractional inhibitory concentrations all <0.5. The way in which one drug potentiates the effect of the other is unclear.

Clinical studies of posaconazole in zygomycosis

Posaconazole is a new broad-spectrum triazole currently available only as an orally administered suspension that has been well tolerated in clinical studies.[22] Bioavailability appears to be satisfactory but this has not been comprehensively investigated in the highest-risk patient groups such as allo-HSCT patients. There are only limited data on its use in children.

There have been two studies of posaconazole for salvage therapy of zygomycosis. Twenty-four patients were recruited from two open-label, non-randomized, compassionate-use studies of posaconazole as salvage therapy of invasive fungal infections.[23] The drug was given as 800 mg daily in divided doses. Complete response was defined as resolution of signs of infection and no relapse within 30 days of stopping posaconazole. Failure was defined as the presence of zygomycosis at the time of stopping posaconazole or at death. The data were assessed by a review committee. At the time of study entry, patients were receiving another systemic antifungal agent, in most cases liposomal amphotericin B. Median duration of treatment was 182 days. Eleven patients had a complete response and eight a partial response. Five cases failed treatment, four of whom died; all failed cases had either haematological or other malignancies. Eighteen patients underwent surgical debridement and this was associated with significantly better survival (P value = 0.02; 95% CI 0.06–0.78). Random trough drug levels were assayed in seven patients who received >14 days therapy. Mean (±SE) concentration was 1.139 (±0.341) mg/L; however, there were insufficient data to correlate serum levels with outcome in individual patients.

In a second compassionate-use study,[24] posaconazole was evaluated for salvage therapy in 91 cases of probable or proven zygomycosis, according to the EORTC defining criteria.[25] The results were submitted by participating investigators on a retrospective basis and then reviewed by an expert panel. Most patients had haematological malignancies or diabetes mellitus. Eleven cases were included that had been reported from the earlier salvage study.[23] Patients had refractory infection, intolerance to the prior antifungal therapy or both. Overall, at 12 weeks, 60% of patients had either a complete or partial response to treatment whereas 17% failed. The remainder had 'stable' disease. Success rates were similar irrespective of site of infection or whether surgical debridement had been performed. The authors concluded that posaconazole is a suitable oral treatment for zygomycosis and suggested that a prospective comparison of posaconazole and lipid amphotericin B should be performed for primary treatment to determine which might have greater efficacy.

Another attractive indication for posaconazole is prophylaxis of invasive fungal infections in high-risk patients such as those undergoing remission induction therapy for acute leukaemia or HSCT. In a neutropenic mouse model of zygomycosis, posaconazole showed comparable prophylactic efficacy to amphotericin B using the criteria of prolongation of survival and reduction of fungal tissue burden in different organs.[26] Interestingly, although

both drugs were effective at reducing fungal burden in organs, this was less so with *Rhizopus oryzae* compared with *A. corymbifera*. Only amphotericin B was effective in reducing the number of fungal foci in the brain.

There have been two recently completed studies of posaconazole prophylaxis of IFI in high-risk patients. One was in neutropenic patients receiving leukaemia chemotherapy,[27] the other in patients following HSCT with severe graft-versus-host disease.[28] Out of a total of 1202 patients who received either posaconazole or comparator drug (either fluconazole or itraconazole), there were only two cases of documented zygomycosis, both in the comparator arms. It is interesting that there were so few cases of zygomycosis in such high-risk patients, and, as a consequence, it is not possible to draw a conclusion on the preventive efficacy of posaconazole for this infection although it should be effective based on the *in vitro*, animal model and other clinical data.

Current management of zygomycosis

Several recent reviews identify factors that are critical to successful treatment of zygomycosis.[2,6,29]

Rapid diagnosis

The starting point is to recognize patients at increased risk and early signs of infection. Initially, clinical features may be similar to those of other invasive mould infections, but it is the consideration of zygomycosis as a diagnosis that may lead to timely confirmation by successful biopsy and/or culture of the causative organism. The patient may complain of a combination of headache, visual disturbance, facial and/or orbital swelling. Urgent radiological imaging to localize and determine the extent of the infection is crucial (although this may initially be falsely negative) and should be followed by surgical review to consider a biopsy, or therapeutic surgical debridement.

Remove or reduce risk factors

The second consideration is to deal with any reversible predisposing factors by, for example, rectifying diabetic ketoacidosis, withdrawing desferrioxamine therapy or reducing the level of immunosuppression.

Antifungal therapy and surgical debridement

Unfortunately, because of the relative rarity of this infection, formal comparative studies of different systemic antifungal agents have not been feasible. Choice of therapy has therefore been based on experience, supplemented by information gleaned from animal model studies and *in vitro* susceptibility data. Historically, the agent of choice was conventional amphotericin B used at higher than normal doses of up to 1.5 mg/kg/day.[1] However, the availability of the less toxic lipid formulations, backed by clinical data to support their use in zygomycosis,[30,31] has led them to become drugs of first choice. Analysis of animal model data, which compared survival benefit and brain drug concentrations, favours liposomal amphotericin B over amphotericin B-lipid complex and amphotericin B.[6] Limited clinical experience also favours liposomal amphotericin B as agent of choice over other formulations of amphotericin B.[32,33] Sometimes, doses in the range 10–15 mg/kg/day have been used, but the optimal dose remains unclear. Posaconazole is now the alternative agent of choice based on the evidence presented above and supported by individual case reports of successful treatment in patients with different underlying conditions.[34–36]

A further consideration is combination antifungal therapy,[37] and there are case reports that describe successful outcomes with combinations of liposomal amphotericin B with either caspofungin or posaconazole, where single agent therapy had failed.[38,39] These encouraging results are supported by animal model data[40] and *in vitro* synergy studies.[22] Surgical debridement should always be considered as an option early in management[6] as the evidence discussed above indicates that this intervention improves survival.

Adjunctive therapies

The role of hyperbaric oxygen (HBO) treatment of zygomycosis has recently been reviewed.[41] In a series of 28 cases, a significant association was found between survival and treatment with HBO ($P = 0.009$) provided patients received an adequate course. Nearly all the patients treated had also received amphotericin B. Survivors were more likely to be diabetic than have a malignancy and to have had the predisposing condition rectified. The authors proposed that comparative studies should be done, with controls, to establish the role of HBO in treatment.

A diabetic patient with advanced cerebral zygomycosis, despite administration of liposomal amphotericin B and surgery, was given salvage treatment with a 7 day course of oral deferasirox, an iron-chelating agent.[42] An MRI scan of the brain 1 week later showed significant improvement. Four months later, the patient appeared to be in remission. Deferasirox, unlike desferrioxamine, does not act as a siderophore for the zygomycetes; indeed it appears to do the reverse with benefit to the host. Clearly this is a very preliminary experience with iron chelation but nevertheless holds promise.

Interferon-γ and granulocyte-macrophage colony-stimulating factor have been shown experimentally to augment zygomycete hyphal damage by polymorphs.[4] *Rhizopus* spp. were found to be less susceptible to the host response than *A. corymbifera*. The authors concluded that further experimental and clinical studies of these potential immunotherapies are warranted.

Transparency declarations

T. R. R. has received funds for speaking at symposia organized on behalf of Pfizer, Merck and Gilead. He is a member of advisory boards for Gilead, Merck and Schering-Plough.

References

1. Sugar AM. Agents of mucormycosis and related species. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 6th edn. Philadelphia: Elsevier, 2005; 2973–84.

2. Chayakulkeeree M, Ghannoum MA, Perfect JR. Zygomycosis: the re-emerging fungal infection. *Eur J Microbiol Infect Dis* 2006; **25**: 215–29.

3. Rees JR, Pinner RW, Hajjeh RA *et al.* The epidemiologic features of invasive mycotic infection in the San Francisco bay area

1992–1993: results of a population-based laboratory active surveillence. *Clin Infect Dis* 1998; **27**: 1138–47.

4. Gil-Lamaignere C, Simitsopoulou M, Roilides E *et al*. Interferon gamma and granulocyte-macrophage colony-stimulating factor augment the activity of polymorphonuclear leukocytes against medically important zygomycetes. *J Infect Dis* 2005; **191**: 1180–7.

5. Shoham S, Levitz SM. The immune response to fungal infections. *Br J Haematol* 2005; **129**: 569–82.

6. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005; **18**: 556–69.

7. Chamilos G, Marom EM, Lewis RE *et al*. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. *Clin Infect Dis* 2005; **41**: 60–6.

8. Chamilos G, Luna M, Lewis RE *et al*. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). *Haematologica* 2006; **91**: 986–9.

9. 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.

10. Sims CR, Ostrosky-Zeichner L. Contemporary treatment and outcomes of zygomycosis in a non-oncologic tertiary care center. *Arch Med Res* 2007; **38**: 90–3.

11. Pagano L, Ricci P, Tonso A *et al*. Mucormycosis in patients with haematological malignancies: a retrospective clinical study of 37 cases. *Br J Haematol* 1997; **99**: 331–6.

12. Tonso A, Ricci P, Cenacchi A *et al*. Invasive infections by filamentous mycetes in adult patients with haematological neoplastic diseases (polycentric and retrospective study of 162 cases). *Haematologica* 1993; **78** Suppl IV: 24.

13. 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.

14. Trifilio SM, Bennett CL, Yarnold PR *et al*. Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. *Bone Marrow Transplant* 2007; **39**: 425–9.

15. 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.

16. Almyroudis NG, Sutton DA, Fothergill AW *et al*. *In vitro* susceptibilities of 217 clinical isolates of zygomycetes to conventional and new antifungal agents. *Antimicrob Agents Chemother* 2007; **51**: 2587–90.

17. National Committee for Clinical Laboratory Standards. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi: Approved Standard M38-A*. NCCLS, Wayne, PA, USA, 2002.

18. Sabatelli F, Patel R, Mann PA *et al*. *In vitro* activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. *Antimicrob Agents Chemother* 2006; **50**: 2009–15.

19. Pfaller MA, Diekema DJ. Rare and emerging opportunistic fungal pathogens: concern for resistance beyond *Candida albicans* and *Aspergillus fumigatus*. *J Clin Microbiol* 2004; **42**: 4419–31.

20. Torres-Narbona M, Guinea J, Martinez-Alarcon J *et al*. *In vitro* activities of amphotericin B, caspofungin, itraconazole, posaconazole and voriconazole against 45 clinical isolates of zygomycetes: comparison of CLSI M38-A, Sensititre YeastOne, and the Etest. *Antimicrob Agents Chemother* 2007; **51**: 1126–9.

21. Guembe M, Guinea J, Pelaez T *et al*. Interaction between posaconazole and caspofungin against clinical zygomycetes: a synergistic effect. *Antimicrob Agents Chemother* 2007; **51**: 3547–8.

22. Kwon DS, Mylonakis E. Posaconazole: a new broad-spectrum antifungal agent. *Expert Opin Pharmacother* 2007; **8**: 1167–78.

23. Greenberg RN, Mullane K, van Burik J-AH *et al*. Posaconazole as salvage therapy for zygomycosis. *Antimicrob agents Chemother* 2006; **50**: 126–33.

24. Van Burik J-A, 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.

25. Ascioglu S, Rex JH, de Pauw B *et al*. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; **34**: 7–14.

26. Barchiesi F, Spreghini E, Santinelli A *et al*. Posaconazole prophylaxis in experimental systemic zygomycosis. *Antimicrob Agents Chemother* 2007; **51**: 73–7.

27. Cornelly OA, Maertens J, Winston DJ *et al*. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59.

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

29. Greenberg RN, Scott LJ, Vaughn HH *et al*. Zygomycosis (mucormycosis): emerging clinical importance and new treatments. *Curr Opin Infect Dis* 2004; **17**: 517–25.

30. Gleissner B, Schilling A, Anagnostopolous I *et al*. Improved outcome of zygomycosis in patients with hematological disease. *Leuk Lymphoma* 2004; **45**: 1351–60.

31. 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.

32. Richardson M. AmBisome: adds to the body of knowledge and familiarity of use. *Acta Biomed* 2006; **77** Suppl 4: 3–11.

33. Revankar SG, Hasan MS, Smith JW. Cure of disseminated zygomycosis with cerebral involvement using high dose liposomal amphotericin B and surgery. *Med Mycol* 2007; **45**: 183–5.

34. Stark D, Milliken S, Marriott D *et al*. *Rhizopus microsporus* var. *rhizopodiformis* sinus-orbital zygomycosis in an immunosuppressed patient: successful treatment with posaconazole after a complicated clinical course. *J Med Microbiol* 2007; **56**: 699–701.

35. Page RL, II, Schwiesow J, Hilts A. Posaconazole as salvage therapy in a patient with disseminated zygomycosis: case report and review of the literature. *Pharmacotherapy* 2007; **27**: 290–8.

36. Rutar T, Cockerham KP. Periorbital zygomycosis (mucormycosis) treated with posaconazole. *Am J Ophthalmol* 2006; **142**: 187–8.

37. Johnson MD, Perfect JR. Combination antifungal therapy: what can and should we expect? *Bone Marrow Transplant* 2007; **40**: 297–306.

38. Vazquez L, Mateos JJ, Sanz-Rodriguez C *et al*. Successful treatment of rhinocerebral zygomycosis with a combination of caspofungin and liposomal amphotericin B. *Haematologica* 2005; **90** (12 Suppl): ECR39.

39. Rickerts V, Atta J, Herrmann S *et al*. Successful treatment of disseminated mucormycosis with a combination of liposomal amphotericin B and posaconazole in a patient with acute myeloid leukaemia. *Mycoses* 2006; **49** Suppl 1: 27–30.

40. Spellberg B, Fu Y, Edwards JE Jr *et al*. Combination therapy with amphotericin B lipid complex and caspofungin acetate of disseminated zygomycosis in diabetic ketoacidotic mice. *Antimicrob Agents Chemother* 2005; **49**: 830–2.

41. John BV, Chamilos G, Kontoyiannis DP. Hyperbaric oxygen as an adjunctive treatment for zygomycosis. *Clin Microbiol Infect* 2005; **11**: 515–7.

42. Reed C, Ibrahim A, Edwards JE Jr *et al*. Deferasirox, an iron chelating agent, as salvage therapy for rhinocerebral mucormycosis. *Antimicrob Agents Chemother* 2006; **50**: 3968–9.