

# AmBisome<sup>®</sup>: adds to the body of knowledge and familiarity of use

*Malcolm Richardson*

Department of Bacteriology & Immunology, University of Helsinki, and Helsinki University Central Hospital, Finland

## Introduction

Liposomal amphotericin B has a wide array of indications and recent data support the ability to escalate the dose in very serious infection. There is an extensive body of knowledge and history of use (familiarity) regarding the use of liposomal amphotericin B which has been published in the scientific and clinical literature since 1990.

The number of publications implies a significant level of use and reflects the number of patients who have been exposed to the drug. So far, over 250,000 patients have been treated.

The case reports presented in this supplement of *Acta Bio Medica* increase the body of knowledge and our familiarity with liposomal amphotericin B. A case report describes and discusses an instance of disease in a patient. The essential characteristic of a publishable case report is its educational value. Some case reports are published because they support the findings in previously published cases or because they are useful reminders of an important point in diagnosis or treatment.

They are by their nature little mysteries that hold readers' interest and take less time to prepare than several other types of papers.

Most case reports fall into one of these five topics: (1) an unexpected association between diseases or symptoms; (2) an unexpected event in the course of observing or treating a patient; (3) findings that shed new light on the possible pathogenesis of a disease or an adverse effect; (4) unique or rare features of a di-

sease; and (5) unique therapeutic approaches or extensions of existing therapeutic practice.

It should be recognized that collecting good evidence can be extremely difficult, even with the best planning. For example, it is clearly not possible to answer all clinical questions with randomized controlled trials. For some questions, the infrequency of the outcomes (requiring large sample sizes), the long natural history of the diseases (requiring long-follow-up periods), variations across patients, and high costs, can all conspire to make a randomized controlled trial impossible.

This review of the disease areas highlighted by the illustrative case histories presented in this Supplement shows background information and examines the contribution made by liposomal amphotericin B in the clinical practice.

## Infection of the paranasal sinuses

*Aspergillus* sinusitis is a worldwide disease; the largest number of cases occur in hot, dry climates. It may be that a hot, dry, dusty climate produces chronic nasal inflammation, allowing an ingrowth and tissue damage by the fungus and its metabolites, followed by the immunologic reaction of the host to the fungal antigens. In hot, dry environments *Aspergillus* infection has a more virulent course.

Aspergillosis of the sinuses includes a number of diseases ranging from a benign noninvasive form to an aggressively invasive type one. There are four basic ty-

pes: saprophytic *Aspergillus* colonization of a previously abnormal sinus, allergic *Aspergillus* sinusitis, subacute or chronic invasive *Aspergillus* sinusitis, and fulminant invasive *Aspergillus* sinusitis.

Aspergillosis is currently the most common fungal infection of the paranasal sinuses. Most patients who have developed *Aspergillus* sinusitis have no underlying disease, although invasive rhinosinusitis has been seen in patients with acute leukemia. There have been only occasional reports of sinus aspergillosis arising in diabetic and leukemic patients. The disease runs a more fulminant course in immunocompromised patients; the mortality has been reported as 100% in bone marrow transplant recipients.

The nose and paranasal sinuses have local factors that may promote fungal infection, including nasal polyps, recurrent bacterial infections, and chronic rhinitis with stagnation of nasal secretions. Some authors have suggested that occlusion of the nasal ostia of the sinuses creates an anaerobic environment that may promote fungal pathogenicity. Other reports have challenged this concept, citing *Aspergillus* infections in such well-aerated regions as the nose, bronchi, and external ear. Other underlying factors include prolonged antibiotic therapy for sinusitis and the greater use of antibiotics and immunosuppressive agents.

Two different forms of sinusitis due to *Aspergillus* spp. have been recognized. Acute sinusitis is a life-threatening condition encountered in immunocompromised patients. The clinical presentation is similar to that of rhinocerebral mucormycosis. The presenting symptoms include fever, nasal discharge, headache, and facial pain. Necrotic lesions develop on the hard palate or nasal turbinates, and disfiguring destruction of facial tissue may occur. The infection can spread into the orbit and brain, causing thrombosis and infarction. Paranasal *Aspergillus* granuloma formation is a slowly progressive condition. It is most common in the tropics, where *A. flavus* is the most frequent cause, although cases have been reported from temperate climates. Affected individuals usually complain of longstanding symptoms of nasal obstruction and headache, suggesting chronic sinusitis, but are otherwise normal. Patients present with unilateral facial pain and headache or with facial swelling and proptosis. The swelling is firm but not usually tender. In the la-

ter stages of this condition, upward spread of the fibrosing paranasal granuloma results in focal cerebral or orbital infection. The typical radiologic finding is a dense filling defect within the maxillary or ethmoid sinuses with erosion of the surrounding bone. This can be confirmed by CT or MRI. A third form of *Aspergillus* sinusitis, termed allergic fungal sinusitis, has recently been described (1). Up to 7% of patients requiring sinus surgery may have allergic fungal sinusitis.

The diagnosis of paranasal sinusitis is nonspecific and often confusing. The differential diagnosis includes bacterial sinusitis, malignant tumors, tuberculosis, syphilis, osteomyelitis, Wegener's granulomatosis, and rhinoscleroma. Treatment for the noninvasive form consists of sinusotomy and curettage of all diseased and necrotic tissue. This treatment is usually curative on its own. The invasive form, however, requires radical surgical debridement and intravenous liposomal amphotericin B. Azole antifungals may have a role in the treatment. Despite these measures, however, multiple recurrences requiring several procedures are the rule.

The treatment of paranasal sinusitis is a conservative surgical drainage. Endonasal approaches to the ethmoid, sphenoid, and frontal sinuses and the Caldwell-Luc approach to the maxillary sinuses are reasonable choices. Systemic antifungals should be avoided unless there is definite evidence of tissue invasion or there is orbital or intracranial invasion.

Further cases of orofacial aspergillosis including maxillary sinusitis have been described (2) emphasizing that invasive *Aspergillus* sinusitis is characterized by rapid spread of the fungus from the sinus airspace into the adjacent structures, especially the brain with a high associated mortality rate.

This and earlier reports emphasize that early diagnosis and aggressive therapy of invasive aspergillosis are critical to achieve optimal therapeutic responses in patients. However, the diagnosis is problematic because of diminished inflammatory response and concomitant infections caused by other organisms. In general, the definitive diagnosis of invasive aspergillosis still requires tissue samples for histological evidence of fungal infection and culture confirmation of *Aspergillus* species. A number of reports have described the utility of antigen detection and molecular methods for enhanced diagnosis. Although culture based methods

are often considered to be the most accurate means of identifying filamentous fungi in tissue specimens, it is not unusual to isolate *Aspergillus* from cultured tissue specimens. Molecular methods employ *Aspergillus*-specific probes to detect DNA in formalin-fixed paraffin-embedded specimens with use of in situ hybridization. It is a promising technique for the rapid and accurate diagnosis of the causative fungus that allows clinicians to select the optimal antifungal agent.

As shown in a number of cases, aggressive surgical debridement and fungicidal antifungals are crucial for the successful management of invasive aspergillus sinusitis (2-5).

### Prophylaxis with AmBisome

AmBisome can be safely administered at dosages fifteen times higher than the conventional drug with the same broad spectrum of activity (6). Increased doses demonstrate non-linear clearance with saturation of the reticuloendothelial system (RES) and redistribution of the drug into non-RES tissues. The efficacy of AmBisome appears to be related both to improved tissue penetration in the lungs, brain, kidneys, liver and spleen along with sustained bioactivity of therapeutic drug levels in these target tissues.

Early studies showed that low-dose AmBisome prophylaxis was effective in children who had undergone bone marrow transplantation (7). Sixty-one children with a median age of six years (range 1-16) were given prophylaxis/therapy for 78 courses of treatment with liposomal amphotericin (AmBisome) and were retrospectively reviewed. Thirty-six received allogeneic bone marrow, 22 a liver transplant, two kidneys and one a liver and kidney. AmBisome was given as prophylaxis in 30 episodes, as treatment for suspected invasive fungal infections (IFI) in 33 patients and for a verified IFI in 15 patients. AmBisome prophylaxis was given for a median of 14 days in a dose of 1 mg/kg/day. The mean dose of AmBisome was 2.1 mg/kg/day (range 0.9-5.0). The mean duration of therapy was 10 days in children with suspected IFI and 20 days in children with verified IFI. The total dose ranged from 0.025 g up to a maximum of 3.95 g. Proven and probable side effects of AmBisome were a de-

crease in the level of serum potassium (30/78 cases), renal toxicity (22), an increase in the alkaline phosphatases (24), back pain (2), fever and abdominal pain (2), anaphylactic reaction (1), an increase in the bilirubin level (1), nausea (1), chest pain (1) and fever (1). In 21 of 31 children with suspected IFI, fever disappeared (68%). In 14 verified or suspected IFI cases treated for 5 days or more, the clinical cure rate was 12 (86%). Eradication of fungi from a deep site was verified in 8/10 and the survival rate from 1 1/2 years to more than 7 years was 7/12 (58%). The authors conclude that AmBisome was well tolerated as prophylaxis and therapy in transplanted children, that few acute toxic side effects were seen and that the cure rate in verified IFI was high.

In a similar setting, paediatric patients undergoing hematopoietic stem cell transplantation (HSCT) Mehta and colleagues hypothesized that once-weekly high-dose AmBisome therapy could provide adequate fungal prophylaxis (8). They performed a pharmacokinetic pilot study to determine whether once-weekly high-dose AmBisome administration would result in effective concentrations throughout the dosing interval. A total of 14 children (mean age, 3 years, 1 month; range, 4.5 months-9 years, 9 months) undergoing HSCT received once-weekly intravenous AmBisome prophylaxis (10 mg/kg as a 2-hour infusion). AmBisome was well tolerated at this dose. The half-life calculated in this pediatric population was shorter on average than reported in adults (45 hours vs 152 hours). The volume of distribution correlated best with body weight, and clearance was best predicted by initial serum creatinine level. Mean (+/- standard deviation) individual plasma trough concentrations were 0.23 (0.13) mg/L after single doses and 0.47 (0.41) mg/L after multiple doses. Mean steady-state area under the curve was higher at week 4 than after a single dose. Single-dose and steady-state pharmacokinetic profiles were similar in eight patients, whereas in four patients the week four profile showed nonlinear elimination. However, plasma concentrations at seven days ( $C_{min}$ ) were not significantly different after the first and fourth doses, suggesting no significant accumulation over the course of therapy. The data show measurable amphotericin B plasma concentrations seven days after high-dose infusion of

AmBisome. The study suggests that once-weekly dosing, may provide useful protection against fungal infections.

AmBisome has been compared with a combination of fluconazole and itraconazole as prophylaxis in patients undergoing induction chemotherapy for acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) (9). The authors evaluated the efficacy and toxicity of liposomal amphotericin B compared with a combination of fluconazole plus itraconazole as prophylaxis in this setting. Patients with newly diagnosed AML or high-risk MDS who were undergoing initial induction chemotherapy were randomized to receive either fluconazole 200 mg orally every 12 hours plus itraconazole tablets 200 mg orally every 12 hours or liposomal amphotericin B (3 mg/kg intravenously 3 times per week) in this prospective, open-label study. Seventy-two liposomal amphotericin B-treated patients and 67 fluconazole plus itraconazole-treated patients were enrolled in the study. Out of these, 47% of patients completed antifungal prophylaxis without a change in therapy for proven or suspected fungal infection. Three patients in each arm developed a proven fungal infection. Twenty-three percent of the liposomal amphotericin B-treated patients and 24% of the fluconazole plus itraconazole-treated patients were changed to alternative antifungal therapy because of persistent fever (P value not significant). Nine percent of the liposomal amphotericin B-treated patients developed pneumonia of unknown etiology compared with 16% of the fluconazole plus itraconazole-treated patients. Infusion-related reactions were noted in five liposomal amphotericin B-treated patients. Responses to chemotherapy and induction mortality rates were similar for the two arms. The authors concluded that liposomal amphotericin B showed the same efficacy as antifungal prophylaxis during induction chemotherapy for patients with AML and MDS. L-AmB was associated with higher rates of increased serum bilirubin and creatinine levels.

Reduced-intensity stem cell transplantation (RIST) has been developed to be a novel curative option for advanced hematologic diseases. Its minimal toxicity allows for transplantation in patients with advanced age or with organ dysfunction. Young patients

without comorbidities can undergo RIST as outpatients. However, fungal infection remains an important complication in RIST. Given the poor prognosis of fungal infection, prophylaxis is critical in its management. The prophylactic strategy is recently changing with the development of RIST (10), moreover, the median day for the development of fungal infection is day 100, when most RIST patients are followed as outpatients. The focus of fungal management after RIST needs to shift from the in-hospital environment to prevention of community acquired infection in an out-patient setting. Various antifungal regimens have recently been developed and introduced for clinical use, including the use of low-dose AmBisome. A major change in prophylactic and maintenance treatment will undoubtedly occur within several years.

The prevalence of fungal infection after orthotopic liver transplantation (OLT) is 5% to 42%. The most common isolated pathogens are *Candida* and *Aspergillus* species. High-risk liver transplant recipients are more susceptible to the development of invasive fungal infections, with prevalence >40% and mortality rates of 78% to 100%. The strategy for fungal prophylaxis in this population has not been defined. Prevention remains an elusive goal, especially for IFI caused by moulds. In a large series of recipients, patients who fulfilled four or more variables identified as risk factors for IFI received a cumulative dose of 1-1.5 g of lipid formulations of amphotericin B (AmBisome or Abelcet) (11). The development of IFI in these patients was compared with historical patients. Two hundred and eighty liver transplant recipients were analysed over a period of 8 years. In the historical group, IFI were observed in 22 out of 131 patients (17%) and invasive aspergillosis in 13 of them (10%). In the study group IFI were observed in nine out of 149 (6%) and invasive aspergillosis in six patients (4%). In patients with four or more risk factors (high risk) for IFI, the administration of AmBisome reduced the risk from 36% to 14%, and the risk of aspergillosis from 23% to 5%. Notably, prophylaxis reduced the risk of aspergillosis from 32% to 0% in dialysed patients. Variables independently associated with IFI in high-risk patients were dialysis and surgical re-intervention, while AmBisome was a protective factor in this multivariate analysis. The analysis in these high-

risk patients was not able to demonstrate an association between the administration of AmBisome and higher survival. The conclusion of this study was that selected risk factors are good predictors of IFI in liver transplant recipients and that the administration of AmBisome in high-risk patients is independently associated with a reduction of IFI.

In a study designed to prospectively evaluate the efficacy of low-dose amphotericin B preparations for the prevention of IFI in high-risk liver transplant recipients patients were recruited and randomised to openly receive intravenously either conventional amphotericin B at a dose of 15 mg daily, or AmBisome 50 mg daily (12). Prophylaxis was continued until discharge from the intensive care unit, until patient death, or until time of conversion to high-dose AmBisome for treatment of suspected or confirmed IFI. During the study period, 360 adult liver transplants were performed; 132 patients were eligible for 149 recruitment episodes into the trial, and 83 patients were recruited for 92 episodes. Out of 92, 48 patient episodes were randomised to receive AmBisome prophylaxis, and 44 to receive conventional amphotericin B. IFI were uncommon, diagnosed for three patients in the AmBisome group, and for two in the conventional amphotericin B group. Furthermore, *Aspergillus* was isolated on a single occasion during 92 episodes of prophylaxis. Fungal colonization scores did not significantly differ between the two groups. There was a significant difference in the rates of survival to ICU discharge between the two groups (79.6% AmBisome vs. 59.5% conventional amphotericin B). Renal function measures including creatinine clearance at the beginning and conclusion of prophylaxis, and at 12 months post transplant were not statistically different between the two groups. The authors concluded that the use of amphotericin B, liposomal or non-liposomal preparations at low doses, for prophylaxis of IFI in high-risk LT patients, was associated with a low incidence of serious fungal infection. Furthermore, the study showed that low-dose AmBisome prophylaxis was associated with an increased likelihood of successful discharge from the ICU.

A second study by Castroagudin and colleagues showed that among 100 consecutive OLT followed for 28 months, 21 recipients (15 men, overall mean

age of 48.5 years, range 23–65 years) were considered to be at high risk for the development of fungal infections when they presented with at least one of the following criteria: acute liver failure, assisted ventilation >7 days, retransplantation, relaparotomy, antibiotic therapy >14 days, transfusion requirements >20 red blood cells units, and/or biliary leakage (13). This group received AmBisome (1 mg/kg/day for 7–10 days). One-year survival in the high-risk group was 80%. Prevalence of invasive fungal infection was 9.5%. No *Candida* infection was observed. Two patients developed *Aspergillus* infection: an abdominal aspergillosis treated with percutaneous drainage and liposomal amphotericin B (5 mg/kg/day) showed a favorable clinical outcome. The other patient who developed brain aspergillosis died 25 days after OLT. Adverse events related to the drug were hypokalemia (n = 2), back pain (n = 3), and renal dysfunction (n = 2). None of these events required withdrawal of the prophylaxis regimen. In this series of patients, prophylaxis with AmBisome in high-risk liver graft recipients showed a low rate of severe fungal infections. However, it is evident that more studies are needed in order to determine the highest risk population and the best drug dosage.

### Cryptococcal meningitis

Two cases of cryptococcal meningitis in AIDS patients reported in this Supplement highlight the importance of the host response in synergy with optimal treatment. Previous reports in the literature explore the possibilities of maintenance treatment with combinations of amphotericin B and fluconazole.

AmBisome is generally unable to pass through the blood-brain barrier, but the distribution of AmBisome in the brain is increased by inflammation, and in consequence, AmBisome exhibits activity against fungal meningitis. Takemoto and colleagues investigated the influence of the progression of cryptococcal meningitis on the brain penetration and efficacy of AmBisome (14). Mice were infected intracerebro-ventricularly with *Cryptococcus neoformans* 4 h or 5 days prior to a single dose treatment. The brain tissue level and efficacy of AmBisome when administered 5 days after

infection were greater than 4 h after infection. An immunohistochemical study showed that AmBisome was localized at the infected site in the subarachnoid space. When AmBisome was compared with amphotericin B deoxycholate at the maximum tolerated dose, 10 mg/kg AmBisome exhibited greater efficacy than 1 mg/kg amphotericin B deoxycholate in both regimens. The authors concluded that the brain penetration of AmBisome was enhanced by the progression of cryptococcal meningitis and correlated with the in vivo activity.

A report from China describes the use of Ambisome to treat nine cases of meningitis or meningoencephalitis by *Cryptococcus neoformans* and 28 cases of other deep fungal infections (15). A retrospective study on conventional amphotericin B was performed as the control. A series of indices was observed including curative effect, fungal clearance rate, course of treatment, daily dose, cumulative dose and adverse effects. Nine cases of cryptococcal meningitis or meningoencephalitis treated with Ambisome were clinically cured with an effective rate of 100%, within a mean course of 50 days, which was shorter than that of conventional amphotericin B, by a mean cumulative dose of 1807.2 mg. Fungal clearance rate on the second month of treatment was 89% with AmBisome, which was higher than that of conventional amphotericin B. Twenty-eight cases of other deep fungal infections treated with Ambisome were clinically cured with an effective rate of 92%, within a mean course of 19.3 days, by a mean cumulative dose of 907.5 mg, and fungal clearance rate on the second and third month was 75 and 92%, respectively. The adverse effects by Ambisome evidently decreased compared with those by conventional amphotericin B.

### Invasive aspergillosis in the setting of tuberculosis

Pulmonary aspergilloma is a recognized complication of pre-existing cavitory lung disease in immunocompetent hosts. The most prevalent pathogens are *Aspergillus fumigatus* and *A. flavus*. The case report by Viggiani and Besozzi in this Supplement describes a patient with an aspergilloma caused by *A. niger* in a setting of tuberculosis. There are a number of other si-

milar cases demonstrating that *A. niger* may be implicated in cavitory disease which may progress to invasive pulmonary disease.

Another case describes a 66-year-old woman who had undergone one year treatment for pulmonary nontuberculous mycobacterial disease due to *Mycobacterium avium*. Five years earlier she was admitted to our hospital because of continuous fever and a newly detected abnormal chest shadow, which was like a fungus ball in the right upper lobe on chest computed tomography in the giant cavitory lesion caused by pulmonary Mycobacterium-avium complex (MAC) disease (16). A diagnosis of chronic necrotizing pulmonary aspergillosis (CNPA) complicated by pulmonary MAC disease was made because *Aspergillus niger* was isolated from several sputum specimens, anti-*Aspergillus* antibody was positive, and clinical symptoms such as fever, were disclosed with the radiological finding of a fungus ball-like shadow and an infiltration shadow around the cavity. The patient had received various forms of antifungal chemotherapy, but the clinical effect had been poor. Since then, she had been slowly worsening. Although mycetomas, with the typical appearance of a fungus ball on a chest radiograph, have been reported to easily form in cavitory lesions caused by previous pulmonary tuberculosis, we believe, as illustrated by the present case, that they could also form in such lesions caused by pulmonary MAC disease, since the frequency of pulmonary nontuberculous mycobacterial disease has recently been increasing in comparison with that of pulmonary tuberculosis.

Gifford and colleagues describe a case of fatal haemoptysis from invasive *A. niger* infection in the setting of bullous lung disease, steroid-treated sarcoidosis, and *Mycobacterium avium* complex infection (17). Even though AmBisome was administered and which resulted in mycological clearance of lung tissue, the patient died from massive haemoptysis. This report highlights the potential for *A. niger* to cause invasive disease in conjunction with other pathologic processes in the lung.

*Aspergillus niger* has been shown to be sensitive to amphotericin B using conidial suspensions, independent of the method used. However, the invasive form of *Aspergillus* is dominated by the appearance of

hyphae. The morphological form of *Aspergillus* against which antifungal agents interact is the hyphal biomass. Impairment of hyphal growth and survival is the ultimate requirement of an effective antifungal agent. It has been found that the MICs of hyphae against lipid-based amphotericin B formulations (AmBisome) and amphotericin B colloidal dispersion (Abelcet) were within three dilutions higher than those against conidia for isolates of *A. niger* (18). This study demonstrates that in order to inhibit the hyphae of *Aspergillus* species in vitro, including *A. niger*, amphotericin B must be “applied” at higher concentrations (up to four-fold) than those required to inhibit conidia. Different composition of the fungal membrane or the quantity of hyphal biomass in comparison with that of conidia could account for the higher resistance of hyphae. Furthermore, this study, showing that higher doses were required to inhibit hyphae, suggests that the maximum tolerated dose of an antifungal should be administered to patients with a probable or proven diagnosis to control the infection. Whether antifungal drug concentrations which inhibit hyphae are achievable in infected tissue is not known. However, it is known that the average tissue concentration of lipid formulations of amphotericin B are two-fold higher than those of conventional amphotericin B (6).

### Mucormycosis in haematological malignancy

The incidence of mucormycosis in patients with haematological malignancies has increased during the last decade, probably due to the more severe and prolonged post-chemotherapy neutropenia. The diagnosis is usually made at autopsy and its incidence in autopsy studies in patients with haematologic malignancies ranges between 0.4 and 0.9%. A number of retrospective studies have been published. Pagano and colleagues reported a series of 37 patients with haematological malignancy (21 acute myeloid leukaemia, 11 acute lymphoid leukaemia, two lymphoma, two hairy cell leukaemia, one Hodgkin's disease) and histologically documented mucormycosis (19). Fever, thoracic pain and cough were the most common presenting symptoms. At the onset, 89% of patients were neutropenic with a mean duration of previous neutropenia of 14

days (range 6–60). The most frequent sites of infection were lungs (81%), CNS (27%), sinus (16%), liver (16%) and orbital space (10%). Only three patients were asymptomatic. A correct in vivo diagnosis was made in only 13 (35%) patients. When performed, thoracic and cranial CT scan were the most useful diagnostic investigations. Despite the fact that 26 febrile patients were treated with empirical antifungal treatment, 28 of the 37 patients (76%) died from fungal infection at a mean time of 17 days from the onset of the clinical symptoms. Nine patients were treated with antifungal therapy plus, in five cases, radical surgery procedures.

The prolonged use of conventional amphotericin B or liposomal amphotericin B in these infections appears to be statistically correlated with a good prognosis. In particular high dose liposomal amphotericin B has been successful in eradicating mucormycosis in patients who had relapsed acute leukaemia, as exemplified by two case reports (20). The first patient with relapsed acute myeloid leukaemia developed a rapidly expanding solitary necrotic neck lesion associated with opacity of maxillary sinus at a time when he was profoundly pancytopenic following high dose chemotherapy. The second patient was a 3-year-old boy with pre-B acute lymphoblastic leukaemia who developed a central nervous system relapse whilst on his first line treatment and was treated with more aggressive chemotherapy. During a period of profound pancytopenia following re-induction therapy, including high dose steroids and prolonged course of antibiotics for proven septicaemia, the patient developed periorbital swelling and proptosis and a clinical diagnosis of rhinocerebral mucormycosis was made. Both patients were treated with high doses of AmBisome. The doses were escalated to 10 and 15 mg/kg/day, resulting in a successful eradication of the disease.

An extensive review of mucormycosis in the setting of haematological malignancies presents an overview of 120 patients from the literature with underlying haematological or oncological disorders (21). This analysis documents the improved survival in sinus (15/17 patients surviving) and cutaneous (6/9 patients surviving) disease. Haematological patients with pulmonary (9/30 patients surviving) or disseminated (4/38 patients surviving) zygomycosis still have a poor prognosis. The clinical course of sinus-orbital

involvement (4/11 patients surviving) follows sinus-cerebral (2/3 patients surviving) or cerebral (3/6 patients surviving) disease. Besides deoxycholate amphotericin B (24/62 patients surviving), patients seem to benefit from AmBisome (10/16 patients surviving) or sequential conventional amphotericin B/AmBisome treatment (6/8 patients surviving). Alternative treatment options lead to success in only a few patients.

Recently, Bethge and colleagues reported the experience of a single center with mucormycosis in patients with haematologic malignancies (22). Mucormycosis were diagnosed in six patients, (mean age of 52 years; range, 26-74) treated between 2001-2004. Diagnoses included acute myeloid leukemia (AML) (n=3), acute lymphoblastic leukemia (n=1), chronic lymphocytic leukemia (n=1) and multiple myeloma (n=1). Mucormycosis was diagnosed in the setting of neutropenic following allogeneic hematopoietic cell transplantation (n=3) or intense chemotherapy (n=3). Sites of infections were rhinocerebral, facial and pulmonary involvement each in one patient and disseminated mucormycosis in three patients. The diagnosis was established by computed tomography followed by surgical interventions and histological diagnosis in four patients and post-mortem in two patients. The species identified were *Rhizopus* (n=3), *Rhizomucor* (n=2) and *Absidia* (n=1). Treatment responses were best if surgical resection was followed by aggressive antifungal chemotherapy. Five of six patients died, all of complications due to mucormycosis or their underlying disease. Only one patient with facial mucormycosis is still alive. The authors experience demonstrates that patients with mucormycosis have a high mortality rate and early recognition followed by aggressive surgical debridement, high dose antifungal therapy and attempts to correct the underlying immunocompromised state are crucial in the treatment of this fatal infection.

## Conclusions

Amphotericin B deoxycholate has been the 'gold standard' treatment for invasive fungal infections for over 40 years. Driven to improve on the renal toxicity

of amphotericin B deoxycholate, extensive pharmaceutical and clinical research has led to the development of several new antifungals including lipid formulations of amphotericin B, broad-spectrum azoles and echinocandins. Compared with amphotericin B deoxycholate, AmBisome has a distinct advantage in that it has improved drug safety, in particular reduced incidence and severity of amphotericin B deoxycholate-related nephrotoxicity. There is now a significant familiarity of use regarding AmBisome. Case reports, equally, contribute to the body of knowledge with additional understanding to provide a rationale to justify substituting amphotericin B deoxycholate with AmBisome.

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Correspondence: Malcolm Richardson,  
Associate Professor in Medical Mycology  
Department of Bacteriology & Immunology,  
University of Helsinki,  
and Helsinki University Central Hospital (Finland)  
E-mail: Malcolm.richardson@helsinki.fi  
www.actabiomedica.it

