Forty-one recent cases of invasive zygomycosis from a global clinical registry


11st Department of Internal Medicine, University of Cologne, Cologne, Germany; 2Medizinische Klinik und Poliklinik II, University Hospital Würzburg, Würzburg, Germany; 3Department of Microbiology, Sri Ramachandra University, Porur, Chennai, India; 4Medizinische Klinik II—Infectious Diseases, University Hospital Frankfurt, Frankfurt, Germany; 5Department of Hygiene, Microbiology and Social Medicine, Innsbruck Medical University, Innsbruck, Austria; 6Haematology and Oncology Department, Hopital de Hautepierre, Strasbourg, France; 7Department of Otolaryngology—Head & Neck Surgery, The Edith Wolfson Medical Centre, Tel-Aviv University, Holon, Israel; 8Infectious Diseases Research Program Centre for Bone Marrow Transplantation and Department of Paediatric Haematology/Oncology, Children’s University Hospital, Münster, Germany; 93rd Medical Department, Universitätsmedizin, Johannes Gutenberg University, Mainz, Germany; 103rd Medical Department—Haematology, Oncology and Palliative Medicine at the University of Rostock, Rostock, Germany; 11Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany; 12Department of Haematology, University Hospital Gasthuisberg, Leuven, Belgium; 13Department of Haematology and Oncology, Ernst-von-Bergmann Clinic, Potsdam, Germany; 14Paediatric Haematology and Oncology, Children’s Hospital Medical Centre, University of Bonn, Bonn, Germany; 15Unit of Infectious Diseases, Rabin Medical Centre at Beilinson Hospital, Tel-Aviv University, Petah-Tiqwa, Israel; 16Institute for Hygiene and Environmental Medicine, Rheinisch-Westfälische Technische Hochschule (RWTH), Aachen, Germany; 17Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN0706, University of Cologne, Cologne, Germany  

*Corresponding author. Klinikum der Universität Köln—Klinik I für Innere Medizin, Kerpener Str. 62, 50937 Köln, Germany. Tel: +49-(0)221-478-6494; Fax: +49-(0)221-478-3611; E-mail: oliver.cornely@ctuc.de  

Received 23 September 2009; returned 23 October 2009; revised 2 November 2009; accepted 9 November 2009  

Background: Invasive zygomycosis accounts for a significant proportion of all invasive fungal diseases (IFD), but clinical data on the clinical course and treatment response are limited.  

Patients and methods: Fungiscope™—A Global Rare Fungal Infection Registry is an international university-based case registry that collects data of patients with rare IFD, using a web-based electronic case form at www.fungiscope.net.  

Results: Forty-one patients with invasive zygomycosis from central Europe and Asia were registered. The most common underlying conditions were malignancies (n=26; 63.4%), diabetes mellitus (n=7; 17.1%) and solid organ transplantation (n=4; 9.8%). Diagnosis was made by culture in 28 patients (68.3%) and by histology in 26 patients (63.4%). The main sites of infection were the lungs (n=24; 58.5%), soft tissues (n=8; 19.5%), rhino-sinu-orbital region (n=8; 19.5%) and brain (n=6; 14.6%). Disseminated infection of more than one non-contiguous site was seen in six patients (14.6%). Mycocladus corymbifer was the most frequently identified species (n=10, 24.4%). A favourable response was observed in 23 patients (56.1%). Overall survival was 51.2% (n=21). At diagnosis, four patients (9.8%) were on continuous antifungal prophylaxis with itraconazole (n=1; 2.4%) or posaconazole (n=3; 7.3%). Initial targeted treatment with activity against zygomycetes was administered to 34 patients (82.9%). Liposomal amphotericin B was associated with improved response (P=0.012) and survival rates (P=0.004).  

Conclusions: Pathogen distribution and, consequently, drug susceptibility seem to vary across different geographic regions. Furthermore, protection from invasive zygomycosis for patients on posaconazole prophylaxis is not absolute. Our findings indicate that the use of liposomal amphotericin B as first-line treatment for patients diagnosed with zygomycoses merits further investigation, preferably in the form of a clinical trial.  

Keywords: invasive fungal diseases, Fungiscope™, antifungal treatment, breakthrough infections
Introduction

Currently, zygomycetes account for an increasing proportion of all invasive fungal diseases (IFD), particularly among patients undergoing chemotherapy or allogeneic haematopoietic stem cell transplantation (HSCT) for a haematological malignancy. Recent results from a prospective registry showed an incidence of 7.2% in this group. Other immunocompromised patients at risk include those using corticosteroids or undergoing solid organ transplantation. Diabetic ketoacidosis, iron overload, use of deferoxamine and long-term antifungal prophylaxis with voriconazole, as well as disruption of the barrier function of the skin, e.g. after trauma or burns, have also been associated with invasive zygomycosis.2–5

Even though no well-designed randomized clinical trials have been conducted to evaluate different treatment approaches, treatment with antifungal drugs in combination with surgical debridement is considered standard. Amphotericin B deoxycholate (D-AMB) remains the only antifungal approved for the treatment of zygomycosis. While amphotericin B lipid complex (ABLC) was associated with a favourable response in 52% of patients in a larger series, liposomal amphotericin B (L-AMB) is another popular option.7–9 Thus, optimal treatment remains to be defined, but options include ABLC or L-AMB at >5 mg/kg daily. Evaluation of posaconazole as salvage treatment for zygomycosis, administered as 4×200 or 2×400 mg/day orally, has yielded response rates of 60% and 79%, respectively.10,11 There is not sufficient clinical evidence to support the use of combination antifungal therapy.

In a large analysis by Roden et al.,12 disseminated, gastrointestinal and pulmonary infection were associated with a particularly poor prognosis, as well as concomitant renal failure and infection with Cunninghamella spp. Survival without any therapy was only 3% as opposed to 70% in patients receiving both surgical debridement and antifungal therapy.

We have developed Fungiscope—a Global Rare Fungal Infection Registry and will examine all cases of invasive zygomycosis from this registry to expand the data on demographics, pathogen distribution, diagnosis, treatment and outcomes of this infection. Most importantly, we aim to provide further data as to the best initial treatment of invasive zygomycoses.

Patients and methods

Study type

Fungiscope is an international university-based case registry that collects demographic, clinical and microbiological data of patients with rare IFD using a web-based electronic case report form (eCRF), which can be accessed via www.fungiscope.net. The survey is hosted by ClinicalSurveys.net, an internet research platform for rare infectious diseases. Case registration is on a voluntary basis. For inclusion in the registry, cases have to have positive cultures or histopathological, antigen or molecular genetic evidence of IFD and the associated clinical symptoms and signs of invasive infection.

The data that are entered onto the registry include demographics, underlying conditions, neutrophil count, concomitant immunosuppressive medications, clinical signs and symptoms of IFD, site of infection, diagnostic tests performed, pathogen identification, antifungal treatment, surgical procedures performed, response to treatment, overall survival, and attributable mortality. All incoming datasets are regularly checked for completeness and queries are made in written form. Follow-up information is repeatedly requested until patients display complete or partial response to treatment, or treatment failure. If follow-up could not be continued to this point, clinical response at last contact with the patient was used for analysis.

For this study, the registry was searched for invasive infections due to zygomycetes. The study was approved by the Ethics Committee of the University of Cologne, Germany.

Definitions

The day of diagnosis was defined as the day on which the first diagnostic procedure identifying a zygomycete was performed. For patients with a diagnosis obtained during post-mortem examination, the day of death was considered to be the day of diagnosis. Isolates were identified at the local microbiology laboratory and collected at the study laboratory for further molecular genetic diagnostics.

Antifungal treatment was analysed using a one-dose-received approach. Empirical treatment was defined as antifungal treatment given prior to the diagnostic procedure that led to establishing a diagnosis of invasive zygomycosis, excluding antifungal prophylaxis. Initial targeted treatment was defined as the first treatment given after the day of diagnosis. A favourable response to therapy was defined as complete or partial clinical response at the end of treatment. Complete, partial, stable response, and failure were used as defined elsewhere.13

Statistical analysis

All statistical analyses were carried out using SPSS software (SPSS, version 16.0; SPSS, Chicago, IL, USA). Differences between the qualitative variables in two groups were analysed by a χ2 test with continuity correction or Fisher’s exact test, as appropriate. A two-sided P value of <0.05 was considered significant. Multivariate analysis was not performed, since the sample size did not appear large enough to yield reliable results.

Results

Demographics

Between January 2006 and April 2009, a total of 41 patients with an invasive zygomycosis were registered. Five patients (12.2%) were paediatric. Patient ages ranged from 2 to 88 years, with a median age of 49 years. There were 28 (68.3%) male subjects. Cases were reported from 15 centres in Germany (n=25; 61%), India (n=5; 12.2%), Austria (n=4; 9.8%), France (n=3; 7.3%), Israel (n=3; 7.3%) and the Netherlands (n=1; 2.4%). The number of cases contributed by individual centres was as follows: Würzburg=9; Chennai=5; Frankfurt=5; Innsbruck=4; Cologne=3; Strasbourg=3; Halon=2; Münster=2; Bonn=1; Heidelberg=1; Leuven=1; Petah-Tiqwa=1; Potsdam=1; and Rostock=1.

Underlying conditions

Information on underlying conditions is given in Table 1. Ten patients (24.4%) presented with multiple risk factors. One patient (2.4%) presented without any underlying condition.

Except for one, all patients after chemotherapy for a haematological malignancy had been neutropenic at the time of diagnosis or within 28 days prior to diagnosis. Haematological
malignancies included acute myelogenous leukaemia (n = 7; 17.1%), acute lymphoblastic leukaemia (n = 3; 7.3%), myelodysplastic syndrome (n = 1; 2.4%), mantle cell lymphoma (n = 1; 2.4%) and natural killer cell precursor leukaemia (n = 1; 2.4%). The only solid tumour was a urinary bladder transitional cell carcinoma (n = 1; 2.4%). Mortality and favourable response to treatment in patients with acute myelogenous leukaemia was 71.4% (n = 5) and 57.1% (n = 4), respectively. For all other haematological malignancies, pooled mortality and favourable outcome was 16.7% (n = 1) and 100% (n = 6), respectively. The patient receiving chemotherapy for a solid tumour survived with a favourable outcome.

Of 12 patients (29.3%) undergoing allogeneic HSCT, 9 (75%) received myeloablative and 3 (25%) received non-myeloablative conditioning regimens. One patient (8.3%) received corticosteroids alone, seven (58.3%) received other immunosuppressives and four (33.3%) received a combination of both. Other immunosuppressives included cyclosporin, methotrexate, mycophenolate mofetil, sirolimus and tacrolimus.

Of seven patients (17.1%) with diabetes mellitus, three (42.9%) were insulin dependent and four (57.1%) were non-insulin dependent.

The four (9.8%) solid organ transplants included heart (n = 1; 25%), liver (n = 1; 25%), lung (n = 1; 25%) and kidneys (n = 1; 25%). All patients receiving solid organ transplantation were on immunosuppressives at the time of diagnosis of IFD. In addition, two patients (50%) received corticosteroids, one in prophylactic and one in therapeutic dosage.

### Table 1. Underlying conditions, associated mortality and treatment response in 41 patients with invasive zygomycosis

<table>
<thead>
<tr>
<th>Underlying conditionsa</th>
<th>n (%)</th>
<th>Mortality [n (%)]</th>
<th>Favourable response [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological or oncological malignancy</td>
<td>26 (63.4)</td>
<td>15 (57.7)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>13 (50)</td>
<td>6 (46.2)</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>solid tumour</td>
<td>1 (3.8)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Allogeneic HSCTb</td>
<td>12 (46.2)</td>
<td>9 (75)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (17.1)</td>
<td>4 (57.1)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>4 (9.8)</td>
<td>0 (0)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Major surgery</td>
<td>4 (9.8)</td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>4 (9.8)</td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>3 (7.3)</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Corticosteroidsc</td>
<td>2 (4.9)</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Haemodialysis for chronic renal failure</td>
<td>2 (4.9)</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Trauma</td>
<td>2 (4.9)</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
</tbody>
</table>

HA: haematopoietic stem cell transplantation.
Superadditive data.
aAll peripheral stem cell transplants.
bExcluding allogeneic HSCT and solid organ transplant recipients.

diagnosis and site of zygomycosis

The sites of infection are shown in Table 2. Of the 24 patients (58.5%) with a pulmonary focus, a chest computed tomography (CT) scan was performed in 22 (91.7%). A halo sign was reported in seven patients (31.8%), an air crescent sign in two (9.1%) and a nodule (with or without halo not further specified) in nine (40.9%). A pulmonary focus was present in 22 out of 26 patients with a malignancy (84.6%).

In total, diagnosis was made by culture in 28 patients (68.3%) and by histology in 26 patients (63.4%); both were present in 15 patients (36.6%). PCR for detection of fungi in addition to culture or histology was performed in nine cases (22%). Zygomycetes were detected in five of these cases (55.6%). All pathogens identified are given in Table 3.

In accordance with the 2008 Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group, 30 patients (73.2%) were diagnosed with proven and 7 patients (17.1%) with probable invasive zygomycosis. The remaining four patients (9.8%) did not meet EORTC criteria. Two (4.9%) of
them presented with positive cultures from debrided deep soft tissue infection, but were lacking histological proof of invasive disease. As clinical criteria for deep soft tissue infection are not listed in the current EORTC/MSG criteria, the categories ‘probable’ and ‘possible’ IFD were not applicable. The other two patients (4.9%) presented with a host factor (allogeneic HSCT and neutropenia after induction chemotherapy for acute myelogenous leukaemia) and positive cultures from bronchoalveolar lavage fluid, but their chest CT scan revealed unspecific infiltrates as opposed to those typical of lower respiratory tract fungal disease. Since no alternative origin of infection was identified in spite of every reasonable attempt to exclude an alternative aetiology having been made, these cases were accepted as invasive zygomycoses.

**Treatment and outcome**

Overall, a favourable response was observed in 23 patients (56.1%). Overall survival was 51.2% (n=21). Mortality attributed to invasive zygomycosis was 36.6% (n=15). Causes of death for the remaining five patients were given as progress of underlying malignancy (n=3; 60%), CNS viral infection (n=1; 20%) and myocardial infarction (n=1; 20%).

Information on breakthrough IFD in patients on antifungal prophylaxis is provided in Table 4.

Detailed information on overall, empirical and initial targeted treatment is given in Table 5. Use of L-AMB as initial antifungal therapy significantly improved the favourable response rate and survival, while additional surgical treatment did not.

**Table 3.** Causative pathogens identified in 41 patients with invasive zygomycosis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycocladus corymbifer</td>
<td>10 (24.4)</td>
</tr>
<tr>
<td>Apophysomyces elegans</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Conidiobolus spp.</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Cunninghamella bertholletiae</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Mucor spp.</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Rhizomucor spp.</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Rhizopus spp.</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Rhizopus homothallicus</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Rhizopus microsporus</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Rhizopus oryzae</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Mucorales (NOS)</td>
<td>12 (29.3)</td>
</tr>
</tbody>
</table>

NOS, not otherwise specified.

Dosages given to patients with a favourable response to L-AMB alone as initial treatment ranged between 2 and 10 mg/kg/day. The average dosage was 5 mg/kg/day and the median was 4.5 mg/kg/day. For one patient (2.4%), L-AMB dosage was not available.

On average, an antifungal agent with activity against zygomycetes was administered 3.4 days after acquisition of the sample that led to the diagnosis (minimum = same day; maximum = 18 days). In seven patients (17.1%), time from sample acquisition to treatment was ≥ 7 days.

Seven patients (17.1%) did not receive any initial targeted treatment with activity against zygomycetes. Two patients (4.9%) had a deep soft tissue infection and were treated by surgical debridement alone. Of these two patients, one (2.4%) experienced a complete and one (2.4%) a stable response. Two patients were initially treated with caspofungin. Both were switched to D-AMB and L-AMB after 2 weeks and 1 week, respectively. Both died from IFD within the following week. One patient (2.4%) died the same day the diagnosis had been established. In two patients (4.9%), diagnosis was made post mortem.

Eleven patients (26.8%) were switched to posaconazole after having received D-AMB or L-AMB. Reasons for this switch were given as follows: failure plus drug toxicity in two cases (18.2%); drug toxicity alone in two patients (18.2%); failure alone in four cases (36.4%); and switch to oral drug for discharge purposes in three patients (27.3%). If only patients who were switched to posaconazole due to toxicity or treatment failure were analysed, a favourable response was observed in five patients.
tality rates, empirical treatment is gaining popularity. 16,25,26

those with invasive zygomycosis, has a profound impact on mor-
explanations for the occurrence of breakthrough infection.

present study, measurements of antifungal plasma concen-
invasive zygomycoses in the control groups does not allow for

centre or geographical region. 5,7,8,10 – 12,15,16

size and with a uniform dataset were restricted to patients with
sive zygomycosis on the basis of a uniform electronic documen-
To our knowledge, this is the largest series of patients with inva-
sary endpoints and other possible confounders.

Discussion

To our knowledge, this is the largest series of patients with inva-
sive zygomycosis on the basis of a uniform electronic document-
an open registration policy with respect to country,
institution and patient group.1 All other case series of significant
underlying conditions. While this study cannot yield any inform-
ation on incidence rates of invasive zygomycosis in different
patient groups, frequency of registration may suggest epidemi-
ob tional tendencies. In the largest subgroup of patients with
malignancies, the lungs could be confirmed as the typical site
of infection, as reported previously.8

Genus and species distribution differed from previous reports. Rhizopus spp., Mucor spp. and Cunninghamella bertholletiae have been mentioned as the most frequently isolated zygomycetes by a number of authors who have focused on patients in North America and Italy.7,8,10,15,16 In our study, Mucorru¨ping was the most commonly identified species, followed by Rhizopus and Mucor spp. The fact that patients in our study were reported from central Europe and Asia might account for this pathogen shift.

Ten patients (24.4%) experienced a breakthrough infection during continuous antifungal prophylaxis (Table 4). Special attention should be paid to the four patients on posaconazole or irtra-
conazole prophylaxis. While both antifungals exhibit some activity against zygomycetes, in vitro data suggest superior activity of posaconazole compared with itraconazole.17,18 In line with these findings, several authors have already reported on breakthrough infections during itraconazole prophylaxis, but to date only four cases of breakthrough zygomycosis during pro-
phylaxis with posaconazole have been identified in the litera-
ture.7,10,11,20 – 22 In two large clinical trials, posaconazole effectively reduced the incidence of IFD and significantly improved overall survival in patients with acute myelogenous leukaemia and myelodysplastic syndrome, as well as attributable survival in patients on immunosuppressives due to severe graft-versus-host disease following allogeneic HSCT. 23,24 Cornely et al.13 and Ullmann et al.25 both observed one case of invasive zygomycoses in their respective control groups. While these studies demonstrated the overall efficacy of posaconazole for antifungal prophylaxis in high-risk patients, the low number of invasive zygomycoses in the control groups does not allow for conclusions concerning its protective effect against these infec-
tions in particular. Unfortunately, in the cases described in the present study, measurements of antifungal plasma concen-
trations were not carried out, meaning that antifungal resistance as well as subtherapeutic antifungal concentrations are possible explanations for the occurrence of breakthrough infection.

As early treatment initiation in patients with IFD, including those with invasive zygomycosis, has a profound impact on mor-
tality rates, empirical treatment is gaining popularity.15,25,26

In our study, receiving empirical treatment with activity against zygomycetes, as opposed to empirical therapy with no activity against zygomycetes, was associated with significantly improved survival. Clearly, this statement is limited by the small number of patients. Nevertheless, considering the lack of satisfying alternative data, it should be discussed. Even though the positive effect of active empirical treatment comes somewhat expected, it may be difficult to carry over into clinical practice. In the febrile neutropenic patient, caspofungin is often preferred over L-AMB, because it was associated with fewer treatment discontinuations due to adverse events in a large clinical trial.27 Due to the results from a major clinical trial by Herbrecht et al.28 patients with clinical symptoms compatible with an invasive aspergillosis combined with the presence of a halo or an air crescent sign on a pulmonary CT scan benefit sig-
nificantly from antifungal treatment with voriconazole. Obviously, this general principle applies to patients at risk of inva-
sive pulmonary zygomycosis as well, while they will not profit from the above-mentioned treatments. Thus, if empirical and pre-emptive strategies are applied according to current guide-
lines, patients with zygomycosis are not covered. This underlines the importance of performing rapid diagnostic measures that may lead to a distinction between Aspergillus spp. and zygomycetes, e.g. the use of CT-guided biopsy of typical pulmonary radiographic signs has been shown to be safe and of great diagnostic value.7,9,10

In this patient population, initial therapy with L-AMB was associated with improved favourable response and survival rates when compared with other treatment modalities. Again, our number of patients is limited, but our findings are supported by those of Pagano et al.7,8 Using univariate analysis, they showed that treatment with L-AMB correlated significantly with recovery from infection. The favourable effect of L-AMB may be explained by findings from Ibrahim et al.31 in diabetic ketoacido-
tic or neutropenic mice with disseminated zygomycosis, mono-
therapy with L-AMB improved time to death as opposed to placebo, while posaconazole monotherapy mediated only a non-
significant trend to improve time to death. At the same time, posaconazole did not reduce tissue fungal burden compared with placebo, whereas L-AMB therapy mediated ~10-fold reductions in kidney and ~30-fold reductions in brain fungal burdens. L-AMB is available as an intravenous formulation, while posaconazole steady-state plasma concentrations are attained at 7–10 days following multiple-dose administration.32 Consequently delays in achieving effective exposure to the drug may account for reduced efficacy.

As opposed to previous findings, surgery alone or in combi-
nation with antifungal therapy was not associated with improved response or survival.8,12 Limited sample size and a possible selection bias towards operating on severely ill patients may have contributed to this finding.

In the absence of randomized clinical trials, registries are an alternative approach to guide clinical decision-making, although they come with certain caveats.33 Primarily, these are reporting bias, sample size, multiple testing for a larger number of secondary endpoints and other possible confounders.

Nevertheless, in the absence of comprehensive information on clinically relevant aspects of invasive zygomycosis, our study can provide meaningful information. The pathogen distri-
bution and, consequently, drug susceptibility seem to vary

(62.5%). Survival was 75% (n=6). All patients who were
switched to posaconazole for discharge from hospital survived
with a favourable outcome.
across different geographic regions. Furthermore, protection from invasive zygomycosis for patients on posaconazole prophylaxis is not absolute. At the suspicion of IFD, immunosuppressed patients should receive a rapid and thorough work-up. Finally, our findings indicate that the use of L-AMB as first-line treatment for patients with the diagnosis of zygomycoses merits further investigation, preferably in the form of a clinical trial.

Acknowledgements
We would like to thank Susanna Proske, Karen Pankraz, Blasius Liss, Axel Hamprecht, Andreas ‘Mop’ Streichardt and the entire team of the Clinical Trials Unit Infectious Diseases II, Cologne, Germany for their ongoing efforts and contributions to Fungiscope™.

Funding
The study was supported by unrestricted grants from Astellas Pharma, Essex/Schering-Plough, Gilead Sciences and Pfizer.

Transparency declarations
M. J. G. T. R. has served on the speakers’ bureau of Schering-Plough/Essex, MSD and Gilead Sciences. W. J. H. has received research grants from Schering-Plough/Essex, has been a consultant to MSD and Schering-Plough/Essex and has served on the speakers’ bureau of Schering-Plough/Essex and Pfizer. V. R. has received research grants from Gilead and Pfizer. C. L.-F. has received research grants from Gilead and Pfizer, has been a consultant to MSD and Pfizer and has served on the speakers’ bureau of MSD, Gilead and Pfizer. R. H. has received research grants from Pfizer, been a consultant to Gilead, MSD, Schering-Plough/Essex and Pfizer, and has served on the speakers’ bureau of Gilead, MSD, Schering-Plough/Essex and Pfizer. G. S. has received research grants from MSD, Pfizer, Astellas, Janssen-Cilag and Schering-Plough/Essex and has been a consultant to MSD. A. J. U. has been a consultant to Basilea, Aicuris, Pfizer, Gilead, MSD, Schering-Plough/Essex and Astellas and has served on the speakers’ bureau of Pfizer, Gilead, MSD, Schering-Plough/Essex and Astellas. J. M. has received research grants from Merck/MSD and Pfizer, has been a consultant to Merck/MSD, Astellas, Bio-Rad, Nektar, Schering-Plough/Essex, Zeneus/Cephalon and Viropharma. G. M. has received research grants from Pfizer, has been a consultant to Merck/MSD, Pfizer and Gilead and has served on the speakers’ bureau of Merck/MSD, Pfizer and Gilead. J. J. V. has served on the speakers’ bureau of Schering-Plough/Essex and MSD/Merck. O. A. C. is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN0706) has received research grants from Astellas, Basilea, Bayer, Genzyme, Gilead, Pfizer, Merck, Optimer, Schering-Plough and Vicuron, has been a consultant to Astellas, Basilea, F2G, Gilead, Pfizer, Merck, Molnlycke, Nektar, Schering-Plough and Zeneus and has served on the speakers’ bureau of Astellas, Gilead, Merck, Schering-Plough, SpePharm and United Medical. All other authors: none to declare.

References


32 FDA. Drugs@FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022003s007lbl.pdf (1 November 2009, date last accessed).