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Treatment of invasive *Candida* and invasive *Aspergillus* infections in adult haematological patients ☆

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ABSTRACT

An increasing incidence of invasive fungal infections is observed in most immunocompromised patients, and especially leukaemia patients. In order to decrease the mortality due to these infections, the clinicians need to optimise their treatment choices for the most common fungal infections observed in this population: invasive aspergillosis and candidiasis. These recommendations have been developed by an expert panel following an evidence-based search of the literature assessing the role of antifungal therapies in the treatment of patients with acute leukaemia or bone marrow transplantation and invasive candidiasis – including candidaemia – and aspergillosis. We present results from a questionnaire on the current practice among experts in Europe, show results of the literature search and provide the panel's recommendations.

1. Introduction

Despite recent improvement, the therapy of invasive fungal infections is still disappointing with a failure rate of nearly 50% in invasive aspergillosis and a 12-week overall death rate exceeding 30% in both invasive candidiasis and invasive aspergillosis.[1,2] New drugs have arrived on the market and this has led to the need for a critical review of the existing data and the development of management guidelines for first line as well as salvage therapy.

2. Methodology

The working group of the ECIL meeting for the treatment of invasive *Candida* and invasive *Aspergillus* infections followed the ECIL committee recommendations (see introductory chapter) and used the following keywords: leukaemia, neutropenia, bone marrow transplantation, haematopoietic stem cell transplantation, peripheral blood stem cell transplantation, aspergillosis, candidiasis, candidaemia. A list of questions, restricted to leukaemic patients and haematopoietic stem cell

☆ The ECIL-1 is a common initiative of the following groups or organisations: Infectious Diseases Working Party of the European Blood and Marrow Transplantation Group (EBMT-IDWP), Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), European Leukemia Net (ELN) (EU Grant number: LSHC-CT-2004), and International Immunocompromised Host Society (ICHS).

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transplant (HSCT) recipients, were proposed by the organising committee and redefined by the working group:

- What is/are the optimal first-line and second-line antifungal therapy(ies) of invasive candidiasis and invasive aspergillosis?
- What is the optimal duration of antifungal therapy for candidaemia and aspergillosis?
- What are the current indications for combination antifungal treatment in candidaemia and aspergillosis?
- Should *in vitro* susceptibility testing be recommended to guide the choice of antifungals in candidaemia and in aspergillosis?

Participants were given a questionnaire prior to the meeting and 38 responses were received and analysed.

The strength of the recommendations and the quality of evidence were scored according to the CDC criteria.[3]

3. Invasive candidiasis

The therapeutic choice is usually a two-step process. The clinician is initially informed that blood cultures are positive for a *Candida* sp. Upon identification, the clinician is informed of the species. The questionnaire and the recommendations took into account that the therapeutic decision was taken before species identification, and then modified according to three main species with different susceptibility profiles: *C. albicans*, *C. krusei* and *C glabrata*.

3.1. *Review of the published data*

Fluconazole, Amphotericin B (AmB) deoxycholate, caspofungin and voriconazole are primary treatment options. Their efficacy has been demonstrated in well-designed randomised studies for non-neutropenic patients (Table 1). In contrast, for the neutropenic host only few data are available. In the large randomised trials, neutropenic patients were either excluded or represented only a small proportion of the cohort, making it difficult to reach the same level of evidence as for the non-neutropenic patients.

3.1.1. *Epidemiological trends*

A shift towards non-*albicans Candida* species such as *C. glabrata* and *C. krusei* with decreased susceptibility or resistance to azoles has been observed in North America and Europe.[4–6] The increasing use of azoles has been reported as cause for this epidemiological shift but remains controversial.[7] *C. glabrata*, the most frequent non-*albicans* species, is susceptible to AmB and to the echinocandins, but shows reduced susceptibility to azoles.[8,9] *C. krusei* is susceptible to AmB, voriconazole and the echinocandins, but intrinsically resistant to fluconazole and itraconazole.[8]

3.1.2. *Lipid formulations of amphotericin B*

There is no large randomised study comparing AmB deoxycholate and its lipid formulations in neutropenic hosts with candidaemia. The disadvantages of AmB deoxycholate are the infusion-related side effects (e.g. chills, fever, hypoxaemia and hypotension), nephrotoxicity and hypokalemia.[10] Although four studies have shown that administration of AmB deoxycholate as a continuous infusion over 24 h with saline loading reduced infusion-related reactions and renal impairment, alternative therapy may be more appropriate in patients with renal insufficiency or concomitant nephrotoxic drugs.[11–14] Lipid formulations of AmB (colloidal dispersion, lipid-complex and liposomal) are better tolerated than AmB deoxycholate and have been used mainly in patients intolerant to AmB deoxycholate or with altered renal function. However, few studies with a limited number of patients have compared the efficacy of AmB deoxycholate with that of lipid formulations in the treatment of neutropenic patients with invasive candidiasis.

In an open randomised study of invasive fungal infections in neutropenic patients, liposomal AmB, 5 mg/kg, was compared with AmB deoxycholate, 1 mg/kg.[15] A mycological

Table 1 – Summary of randomised first line therapy trials in invasive candidiasis

Ref.	Infection	Antifungal	Total patients	No. of successes (%)	Definition of success
22	Candidaemia	Fluconazole	103	72 (70)	Clinical and microbial response
		Amphotericin B deoxycholate	103	81 (79)	
18	Invasive candidiasis	Fluconazole	75	48 (64)	Clinical and microbial response at the end of therapy
		Amphotericin B deoxycholate	67	44 (66)	
21	Candidaemia	Fluconazole	50	25 (50)	Clinical and microbial response
		Amphotericin B deoxycholate	53	31 (58)	
25	Candidaemia	Caspofungin	109	80 (73)	Clinical and microbial response at the end of intravenous therapy
		Amphotericin B deoxycholate	115	71 (62)	
2	Candidaemia	Voriconazole	248	101 (41)	Clinical and microbial response at week 12
		Amphotericin B followed by fluconazole	122	50 (41)	

response of documented yeast infection was seen in 3/5 patients treated with liposomal AmB versus 0/2 treated with AmB deoxycholate.

A retrospective review of five phase I–II trials investigated safety and efficacy of AmB colloidal dispersion (ABCD).[16] Neutrophil status was not known for all patients. The overall response defined as clinical response with negative blood cultures was 39% (7 of 18 patients) for neutropenic compared to 79% (26 of 33) for non-neutropenic patients. Twenty three of 49 (47%) bone marrow transplant recipients responded successfully as compared to 24 of 39 (62%) non-transplanted patients.

A registry allowed collection of data on 124 patients treated in first and second lines with AmB lipid complex for an invasive candidiasis in the setting of a haematological malignancy or a HSCT.[17] Sixty-one (49%) of the patients responded favourably to the therapy with similar response rates in *C. albicans* and in non-*albicans Candida* infections. Neutropenic status was not stated.

3.1.3. *Fluconazole*

For decades, AmB deoxycholate had been the treatment of choice for invasive candidiasis. In three randomised studies, an observational study, a matched cohort study and in a retrospective study, fluconazole demonstrated similar effectiveness as AmB deoxycholate in patients with candidaemia (Table 1).[18–22] However, only the retrospective analysis included 217 (46%) neutropenic episodes of a total of 476 episodes (Table 2).[20] The patient population of this study formed the basis of a randomised trial and a matched cohort study.[18,19] A success rate of 53% was observed with AmB deoxycholate and 76% with fluconazole. Initial therapy, AmB deoxycholate or fluconazole, was not associated with outcome in a multivariate analysis. A successful outcome, defined as complete resolution of all clinical and laboratory signs of *Candida* infection, was observed in 96 (44%) neutropenic and in 186 (72%) non-neutropenic episodes. Unfortunately, number of neutropenic patients belonging to fluconazole or AmB deoxycholate group is not stated. Overall 3-month mortality was 52%, higher in neutropenic (63%) than in non-neutropenic patients (43%).

3.1.4. *Voriconazole*

A large randomised study investigated the efficacy of voriconazole versus AmB deoxycholate followed by fluconazole after species identification and antifungal susceptibility testing in non-neutropenic patients with candidaemia and showed an equal efficacy of both treatment regimens (Table 1).[2] Success rate defined as clinical cure and mycological eradication was equal in both treatment regimens (41%) with significantly less serious adverse events in the voriconazole group (46% versus 57%).

The compassionate use programme of voriconazole as salvage therapy for invasive candidiasis included 13 neutropenic patients with a favourable response in 6 (46%) of them.[23] A similar number of neutropenic patients have been treated for a baseline fungal infection in trial for persistent febrile neutropenia.[24]

3.1.5. *Caspofungin*

Two randomised studies compared caspofungin to AmB deoxycholate or to liposomal AmB in invasive candidiasis and in empiric therapy of febrile neutropenia, respectively (Table 1).[25,26] Overall only 48 neutropenic patients with invasive candidiasis were treated in these two trials (Table 2). A post hoc analysis of the candidaemia study[25] including only

Table 2 – Summary of main trials for first line therapy of candidaemia in neutropenic patients

Ref.	Infection	Study design	Antifungal	Total patients	Neutropenic patients with candidiasis		Definition of success
					No. of patients	No. of successes (%)	
20	Candidaemia	Retrospective	Fluconazole or amphotericin B deoxycholate	476[a]	217[a]	96 (44%)[a]	Clinical and microbial response
10	Febrile neutropenia	Randomised	Amphotericin deoxycholate	344	11	8 (73)	Composite criteria
			Liposomal amphotericin B	343	11	9 (82)	
25	Candidaemia	Randomised	Caspofungin	109	14	7 (50)	Clinical and microbial response
			Amphotericin B deoxycholate	115	10	4 (40)	
24	Febrile neutropenia	Randomised	Voriconazole	415	13[b]	6 (46)[b]	Composite criteria
			Liposomal amphotericin B	422	6[b]	4 (67)[b]	
26	Febrile neutropenia	Randomised	Caspofungin	556	12	8 (67)	Composite criteria
			Liposomal amphotericin B	539	12	5 (42)	

a Number of neutropenic patients belonging to fluconazole or amphotericin deoxycholate group is not stated.
b Voriconazole group : 13 patients with fungal infection at baseline including 10 candidiasis, 2 aspergillosis and 1 zygomycosis. Liposomal amphotericin B group: 6 patients with fungal infections at baseline including 3 candidiasis, 2 aspergillosis and 1 *Trichoderma* fungemia.

cancer patients showed response rates of 70% in caspofungin-treated and 56% in AmB deoxycholate-treated patients, with the lowest rates for both treatment groups in neutropenic leukaemic patients.[27]

3.1.6. *Micafungin*

Results of a large randomised, double-blind trial compared micafungin and liposomal AmB for the treatment of invasive candidiasis. The results were available in an abstract form after the meeting was held.[28] Success rates were similar in both arms: 89.6% ($n = 202$) and 89.5% ($n = 190$), respectively, with similar efficacy rates for *C. albicans*, *C. parapsilosis*, *C. tropicalis* or *C. glabrata* infections. Responses according to the neutrophil status have not yet been presented.

3.1.7. *Anidulafungin*

Results of a randomised trial comparing anidulafungin and fluconazole in invasive candidiasis have been presented orally after the meeting was held.[29] Success rates were 75.6% for anidulafungin treated-patients ($n = 127$) and 60.2% for fluconazole treated-patients ($n = 118$) at the end of intravenous therapy ($p = 0.01$). Anidulafungin remained significantly superior to fluconazole after adjusting for the following baseline characteristics: immunosuppressive therapy, diabetes mellitus, prior azole therapy, baseline *C. glabrata* and catheter removal. At 6 weeks follow-up, the success rates were 55.9% and 44.1%, respectively. Only 3 and 4 four neutropenic patients have been included in the anidulafungin and fluconazole arm, respectively (Pfizer data on file).

3.1.8. *Catheter removal*

The consensus opinion in the general population of patients with candidaemia is that the existing central venous lines should be removed, when feasible.[30] Fungemia with *C. parapsilosis* has been shown to be more frequently associated with use of catheter than infection with other species.[20] In neutropenic patients, the gastrointestinal tract is a frequent source of candidaemia and it appears difficult, on an individual basis, to determine the relative contributions of the catheter as the source of the candidaemia.[31,32] Previous chemotherapy or corticosteroid therapy and dissemination of the infection have been associated with a non-catheter source for the candidaemia in cancer patients.[32] Catheter removal within 72 h after the onset of candidaemia improved response to antifungal treatment exclusively in patients with catheter-related candidaemia.

3.1.9. *Optimal duration of therapy of invasive candidiasis*

Duration of treatment should be long enough to avoid recurrence of infection and eradicate occult sites of haematogenous dissemination. However, shortening the treatment duration is often advocated to reduce costs, toxicity and the emergence of resistant organisms. Recent guidelines suggest that non-neutropenic patients with candidaemia should be treated for 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection.[30,33] Duration of therapy should be prolonged in case of organ dissemination.[34,35]

International guidelines propose that in the setting of neutropenia, antifungal treatment be continued for 14 days after the last positive blood culture, resolution of signs and symptoms and recovery from the neutropenia.[30] Following neutrophil recovery, ophthalmic examination, ultrasonography, CT-scan or MRI should investigate the possibility of ocular and hepatosplenic candidiasis. If hepatosplenic candidiasis is confirmed, antifungal therapy should be given for at least 6 weeks and up to 1 year,[34] or until resolution or calcification of the lesions.[30]

3.1.10. *Role of susceptibility testing in invasive candidiasis*

The increasing frequency of *Candida* isolates resistant to one or several antifungal agents has propelled interest in antifungal susceptibility testing and its correlation with response to therapy. Like antimicrobial susceptibility testing, the main goal of such testing should be to provide help to the physician by predicting clinical response, or at least forecasting failure.[36]

The possibility of microbiological resistance must always be considered when a patient has previously been treated with an azole or when *C. krusei* or *C. glabrata* are identified. The identification of the species already guides the physician in the choice of antifungal therapy. The existing guidelines remind us that antifungal susceptibility testing is not yet standard of care unlike for antibacterials.[30] The authors consider antifungal susceptibility testing to be most helpful in infections with non-*albicans Candida*, and to support the switch to an oral azole for long-term therapy.

Studies attempting to correlate *in vitro* antifungal susceptibility testing results and outcome were conflicting.[37–43] More convincing results were obtained with fluconazole and voriconazole. Two studies suggested that the dose of the fluconazole be taken into account together with the MIC.[37,44] In a homogeneous population of cancer patients, strictly defined inadequate antifungal therapy appeared to correlate with poor outcome.[37] A recent study on the 249 patients infected with *Candida* sp. and treated with voriconazole in various phase III trials showed a correlation between high MIC (>4 μg/mL) and low response rate (<60%).[45]

3.2. *Questionnaire*

Caspofungin was most often prescribed for first-line therapy in invasive candidiasis before species identification in allogeneic (36%) and autologous (35%) HSCT and in leukaemic patients (39%) (Fig. 1). Fluconazole was preferred by 16%, 25% and 29% of the experts, respectively.

A lipid-based (mostly liposomal) AmB was prescribed before species identification by 31% in allogeneic HSCT patients far before AmB deoxycholate (8%). Lipid-based and deoxycholate AmB were similarly used in autologous HSCT and in leukaemic patients. Voriconazole and itraconazole were only prescribed by a few before species identification whatever the host group.

Fluconazole was the preferred agent for *C. albicans* infections for 69% after species identification. For more than 40%, caspofungin was the preferred agent for *C. glabrata* and *C. krusei* infections before AmB deoxycholate and lipid-based

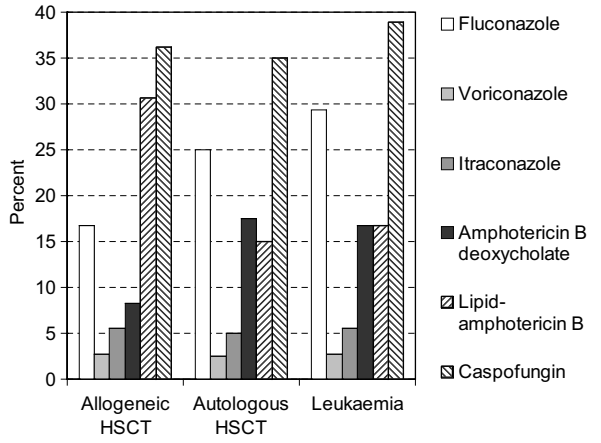

Fig. 1 – Survey on current practice: preferred first line therapy for invasive candidiasis before species identification (38 responses).

AmB (16–20%). Voriconazole was prescribed by 8–11% of the experts.

3.3. *Recommendations*

The main objective of the meeting was to provide guidelines for the management of patients with haematological malignancies. This patient population represents only a small percentage of the patients included in invasive candidiasis trials. There is therefore a need for two sets of recommendations, one for the overall population and another for the subgroup of patients with haematological malignancies.

Guidelines for treatment before species identification are listed in Table 3, and guidelines for treatment after species identification are listed in Table 4. In well-designed randomised studies in non-neutropenic patients, fluconazole, AmB deoxycholate, caspofungin and voriconazole proved to be equal for efficacy and are given grade AI for first line treatment of invasive candidiasis before identification.[2,22,25] AmB deoxycholate is generally not recommended in patients on concomitant nephrotoxic drugs (grade DIII) and never recommended in patients with renal insufficiency (grade EIII).

Anidulafungin and micafungin have been provisionally graded AI and AII, respectively, for the general population of patients with candidaemia on the basis of the studies presented after the meeting was held. Data in neutropenic patients are insufficient or have not yet been presented in detail.

Data are lacking for itraconazole and posaconazole and therefore these two agents have not been graded for candidiasis.

Table 3 – Strength of recommendation and quality of evidence for antifungal agents in candidaemia before species identification

Agent	Overall population[a]	Patients with haematological malignancies and neutropenia
Fluconazole	AI	CIII DIII if azole prophylaxis or colonisation with *C. glabrata* EIII if colonisation with *C. krusei*
Amphotericin B deoxycholate	AI[b]	CIII[b]
Lipid-amphotericin B	AII	BII
Caspofungin	AI	BII
Voriconazole	AI	BII

a Overall population at risk for candidaemia not restricted to haematologic or neutropenic patients.
b DIII if concomitant nephrotoxic drug and EIII if renal impairment.

Table 4 – Strength of recommendation and quality of evidence for antifungal agents in candidaemia in haematologic patients when *C. albicans*, *C. glabrata* or *C. krusei* is identified

Agent	Overall population	Patients with haematological malignancies and neutropenia
Fluconazole	AI for *C. albicans* CIII for *C. glabrata* EIII for *C. krusei*	CIII for *C. albicans* DIII for *C. glabrata* EIII for *C. krusei*
Amphotericin B deoxycholate	AI[a] for *C. albicans* BI[a] for *C. glabrata* BI[a] for *C. krusei*	CIII[a] for *C. albicans* CIII[a] for *C. glabrata* CIII[a] for *C. krusei*
Lipid-amphotericin B	AII for*C. albicans* BII for *C. glabrata* BII for *C. krusei*	BII for *C. albicans* BII for *C. glabrata* BII for *C. krusei*
Caspofungin	AI for *C. albicans* BI for *C. glabrata* BI for *C. krusei*	BII for *C. albicans* BII for *C. glabrata* BII for *C. krusei*
Voriconazole	AI for *C. albicans* CIII for *C. glabrata* BI for *C. krusei*	CIII for *C. albicans* CIII for *C. glabrata* CIII for *C. krusei*

a DIII if concomitant nephrotoxic drug and EIII if renal impairment.

3.3.1. *Candidaemia in haematologic patients before species identification (Table 3)*

Few data are available in haematological and/or neutropenic patients, making strong recommendations for this specific population much more difficult. Fluconazole may not be appropriate in neutropenic patients because of prior exposure to fluconazole as prophylaxis and to the reported shift to non-*albicans* strains in this population.[46–48] The quality of evidence to support the use of lipid AmB, caspofungin or voriconazole in neutropenic patients is based on limited clinical data and on expert opinions.

3.3.2. *Candidaemia in haematologic patients when C. glabrata or C. krusei is identified (Table 4)*

Fluconazole is not recommended for *C. krusei* infection and generally not recommended for *C. glabrata* infection. Caspofungin is the agent of choice for these *Candida* infections. Although AmB is active against *C. glabrata* and *C. krusei*,

AmB deoxycholate is only considered as an option for first line therapy because of its nephrotoxicity and infusion-related side-effects. Voriconazole may be considered an alternative for *C. krusei* infection and *C. glabrata*. When the patient is clinically stable and is able to take oral medication, a switch to oral voriconazole can be considered if the isolate is susceptible (CIII).

3.3.3. *Catheter removal*

Removal of the central venous line is a consensus recommendation for the non-haematological patients with candidaemia (AII). In neutropenic or leukaemia patients, the quality of evidence is looser but in our opinion the existing catheters should be removed (BIII). Removal is always strongly recommended when *C. parapsilosis* is isolated (AII).

3.3.4. *Optimal duration of therapy of invasive candidiasis*

In the absence of a study specifically addressing the question of duration of therapy of candidaemia in leukaemic patients, our recommendations are

- non-neutropenic adults should be treated 14 days after the last positive blood culture and resolution of signs and symptoms (BIII);
- neutropenic patients should receive antifungals for 14 days after the last positive blood cultures and resolution of signs and symptoms and resolved neutropenia (CIII).

3.3.5. *Role of susceptibility testing in invasive candidiasis*

Our recommendation is to perform susceptibility testing in haematological patients on isolates from blood or normally sterile sites, in order to

- evaluate a possible cause of lack of clinical response or microbiologic eradication (AII) and support a change in initial antifungal therapy (BII);
- support a switch from a IV antifungal to an oral azole (AII).

4. Invasive aspergillosis

4.1. *Review of the published data*

Drugs active against *Aspergillus* species include AmB deoxycholate and its lipid formulations, itraconazole, voriconazole, posaconazole and caspofungin. Only 4 randomised studies in primary therapy have been identified (Table 5).[1,15,49,50] Results of a fifth randomised trial comparing two doses of liposomal AmB were presented shortly after the meeting and are therefore not included in the table, but are commented below.[51]

4.1.1. *Amphotericin B formulations*

AmB deoxycholate has been considered as the gold standard of the therapy of invasive aspergillosis for more than three decades. However, clinical data demonstrate efficacy in approximately one third of the patients.[52–55] AmB deoxycholate is associated with significant side effects and renal toxicity.

No data demonstrate convincing superiority in efficacy of liposomal AmB over AmB deoxycholate for the primary treatment of aspergillosis. A pooled analysis of three trials[15,50,56] and a compassionate use, multicenter study was performed applying the EORTC-MSG diagnostic criteria for case selection.[57] The response rate to liposomal AmB was 47% in 61 cases of proven/probable invasive aspergillosis. A randomised trial (whose results were presented after the meeting was held) demonstrated in 201 patients that a standard daily dose of 3 mg/kg was as effective as and better tolerated than a high daily dose of 10 mg/kg for primary therapy.[51] Response rate at end of the randomised therapy was 50% and 12-week survival rate was 72% in the standard dose arm.

AmB colloidal dispersion (6 mg/kg/d) was compared to AmB deoxycholate for primary therapy in a randomised double-blind trial, including 174 patients.[49] Similar low response rates were noted in both arms. The objective response rates were 13% and 15%, respectively.

Data for AmB lipid complex come from open-labelled emergency use programmes for salvage therapy and from a registry for first line therapy.[58–60] These studies were not comparative and therefore were less useful. However, a large number of cases were collected for the registry and efficacy was documented in 47% of 139 cases as first-line therapy and 44% of 216 cases as salvage therapy.[60] Survival data are not available.

Safety profiles of the various lipid-based AmB differ with respect to immediate tolerance. Liposomal AmB proved to be better tolerated than AmB lipid complex in a double-blind randomised comparison in empiric therapy of febrile neutropenia.[61] AmB colloidal dispersion given at 6 mg/kg/d was associated with a higher frequency of immediate adverse

Table 5 – Summary of the randomised trials for first-line therapy of invasive aspergillosis published as full papers up to 31st December 2005

Ref.	Antifungal agents	No. of patients	Success rate (%)	Survival (%)	Significant difference
1	Voriconazole	144	53	71	Yes (p = .02)
	Amphotericin B deoxycholate	133	32	58	
49	Amphotericin B colloidal dispersion	88	13	40	No
	Amphotericin B deoxycholate	86	15	27	
15	Liposomal amphotericin B	26	69	81	No
	Amphotericin B deoxycholate	29	59	62	
50	Liposomal amphotericin B (1 mg/kg/d)	41	58[a]	41	No
	Liposomal amphotericin B (4 mg/kg/d)	46	54	33	

a CR + PR + stabilisation.

Table 6 – Strength of recommendation and quality of evidence for antifungal agents in primary therapy of invasive aspergillosis

Agent	Grading
Voriconazole	AI
Amphotericin B deoxycholate	DI
Liposomal amphotericin B	BI[a]
Amphotericin B lipid complex	BII
Amphotericin B colloidal dispersion	DI
Caspofungin	CIII
Itraconazole	CIII[b]
Combination therapy	DIII

a Provisional grading based on studies presented up to 31st December 2005.
b Start with intravenous formulation.

Table 7 – Strength of recommendation and quality of evidence for antifungal agents for salvage therapy of invasive aspergillosis

Agent	Grading
Voriconazole	BII[a]
Liposomal amphotericin B	BIII[b]
Amphotericin B lipid complex	BIII[b]
Caspofungin	BII[b]
Posaconazole	BII[b]
Itraconazole	CIII[b]
Combination therapy	
Caspofungin + lipid amphotericin B	CIII
Caspofungin + voriconazole	CIII
Amphotericin B + voriconazole	No data

a If not used for primary therapy.
b No data in failures of voriconazole.

events than AmB deoxycholate.[49] With respect to nephrotoxicity, all forms were safer than AmB deoxycholate but induced a doubling in serum creatinine in more than 10% of the patients[49,51,60,61] (see Tables 6 and 7).

4.1.2. *Azoles*

Only limited data are available on itraconazole in invasive aspergillosis. Denning et al. reported the results of oral itraconazole in 76 patients with various underlying conditions.[62] Overall objective response rate was 39%. A strategy using intravenous itraconazole followed by the oral formulation was assessed in 31 patients with a successful response rate of 48%.[63]

Voriconazole was assessed in two open-labelled studies and response rates of 44% and 48% were reported.[64,65] Superiority of voriconazole over AmB deoxycholate was demonstrated for efficacy, safety and survival in a randomised trial.[1] Voriconazole proved to be superior to AmB deoxycholate irrespective of the host group, site of lesion and neutropenic status. Analysis of a series of 81 cases of cerebral aspergillosis treated with voriconazole showed a 35% response rate with a 31% survival.[66] This study underscored the critical role of surgical resection of the lesion. The role of voriconazole in bone or joint aspergillosis has also been investigated in retrospective analysis of 20 patients with a 55% response rate.[67] Very limited data are available on other extra-pulmonary *Aspergillus* infections. *A. terreus*, poorly sensitive to AmB, is susceptible *in vitro* to voriconazole. A review of its interest in *A. terreus* confirmed an improved outcome as compared to patients who received another agent.[68]

Oral posaconazole has been assessed in salvage therapy of various invasive fungal infections, including a cohort of 107 patients with aspergillosis.[69] Comparison with an external control group of 86 cases showed a 42% favourable response rate in posaconazole-treated patients and a significant improved survival as compared to the external control group.

4.1.3. *Echinocandins*

Caspofungin has mainly been assessed in salvage therapy. A non-comparative trial was conducted in 83 patients refractory or intolerant to standard therapy.[70] The overall response rate was 45%, but only 26% in neutropenic patients and 14% in allogeneic HSCT recipients. Similar response rates (44%) were reported in 48 patients receiving caspofungin on a compassionate basis.[71] Candoni et al. have treated 32 patients, including 8 HSCT recipients, with proven or probable invasive aspergillosis in first-line with caspofungin.[72] A favourable response was seen in 56% of the patients. Safety profile of caspofungin is excellent with minimal drug-related toxicity.

4.1.4. *Combination therapy*

Combination therapy has been proposed in the therapy of the most severe invasive fungal infection, including invasive aspergillosis. The most common rationales for combination therapy are an expected synergy with complementary targets within the fungal cells, an increase of the spectrum of action and complementary pharmacokinetic or pharmacodynamic characteristics.[73] While most data demonstrated synergy or additive effects in both *in vitro* and *in vivo* experimental models, no prospective comparative clinical trial has so far been published on combination therapy in first-line or salvage therapy. Non-comparative studies provide controversial results. Success rates ranging from 21% to 60% have been reported.[74–76] A combination of voriconazole and caspofungin given as salvage therapy after failure of AmB provided a substantial improved 3-months survival in allogeneic HSCT recipients compared with voriconazole monotherapy in a historical control group.[77]

4.1.5. *Susceptibility testing*

Filamentous fungi are not routinely tested for susceptibility. Despite controversial results, no correlation between *in vitro* susceptibility to AmB and *in vivo* outcome was convincingly demonstrated in murine models.[78–80] Correlation between *in vitro* and *in vivo* resistance of *A. fumigatus* to itraconazole needs careful selection and standardisation of test conditions to generate reproducible data.[81] Lass-Florl et al. correlated susceptibility to AmB and survival in 6 patients.[82] Twenty two of 23 patients with a resistant strain died. Correlation between failure to AmB and infection with *A. terreus* has been demonstrated.[82–84] Data are lacking for the new antifungal agents (see Fig. 2).

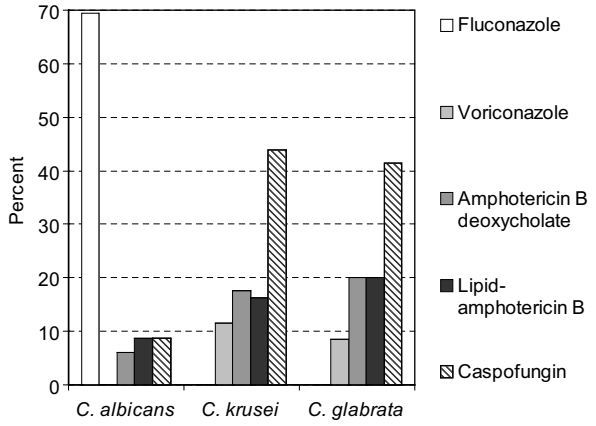

Fig. 2 – Survey on current practice: preferred therapy for invasive candidiasis after species identification (38 responses).

4.2. *Questionnaire*

Voriconazole was the preferred first line therapy for invasive aspergillosis for >60% (Fig. 3). Lipid-based (mostly liposomal) AmB was the second choice for allogeneic HSCT recipients, while AmB deoxycholate and lipid-based AmB were similar choices for autologous HSCT and leukaemic patients. Caspofungin was selected by a very few. Combination first-line therapy was only rarely chosen.

Circumstances leading to the use of combinations were mainly central nervous system infections (90%), other disseminated infections and extensive pulmonary infections. In combination therapy, voriconazole plus caspofungin was the preferred option (45%) followed by caspofungin plus AmB (mostly liposomal form) (39%), and voriconazole plus AmB (mostly liposomal) (24%).

For second-line therapy, the answers were equally distributed between monotherapy and combination therapy. Caspofungin was the preferred monotherapy option (50–75%). Voriconazole was chosen as second line therapy by 25–35% and liposomal AmB by 15–18%. When combinations were chosen for second-line therapy, voriconazole plus caspofungin was the most frequent choice (40%) followed closely by caspofungin plus AmB, mostly in liposomal form (35%).

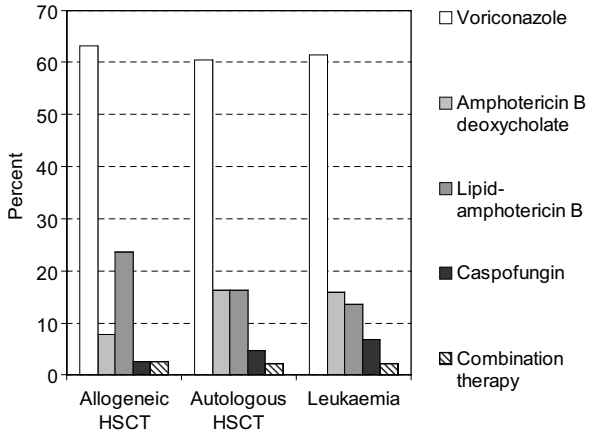

Fig. 3 – Survey on current practice: preferred first line therapy for invasive aspergillosis (38 responses).

4.3. *Recommendations*

4.3.1. *Primary therapy*

Voriconazole is strongly recommended for pulmonary invasive aspergillosis (Table 4). It can be assumed that voriconazole is also recommended for extra-pulmonary infections, including central nervous system aspergillosis. There are insufficient data for recommendations of when to initiate oral treatment. In addition, oral dosing not adapted to weight may lead to suboptimal therapy. Intravenous voriconazole administration is contra-indicated in renal insufficiency.

AmB lipid complex was given the score BII. Based on the data of Cornely et al. presented after the meeting,[51] the committee decided to give a provisional grade BI to liposomal amphotericin B. Liposomal AmB and AmB lipid complex represent an alternative when voriconazole is contra-indicated.

AmB colloidal dispersion is generally not recommended due to poor general tolerance and low objective response rates in a randomised study. AmB deoxycholate is generally not recommended.

Caspofungin and itraconazole have been graded CIII for first-line therapy because of insufficient data in this setting. Combination therapy is generally not recommended in first line. Posaconazole has not been scored in the absence of data in first line therapy.

4.3.2. *Salvage therapy*

Caspofungin and posaconazole were similarly graded. Liposomal AmB, AmB lipid complex and itraconazole were graded on the basis of expert opinions. No data are available for any of these agents in the event of voriconazole failure.

Voriconazole was graded for salvage therapy provided the patient had not received this agent in first-line. Combinations of caspofungin and voriconazole or caspofungin and a lipid-based AmB were scored as an option. In the absence of data, a combination of AmB and an azole was not scored.

4.3.3. *Optimal duration of therapy*

Therapy must be long enough to achieve complete response and to allow recovery from immunocompromised conditions. No fixed duration can be proposed.

4.3.4. *Susceptibility testing*

Aspergillus should not routinely be tested for susceptibility. They should be identified to the species level because this gives useful information for therapy, especially in *A. terreus* infections (CIII).

4.3.5. *Surgery*

Surgery should be considered when a pulmonary lesion is contiguous with a large vessel, in case of haemoptysis from a single lesion and on a case by case basis in localised extra-pulmonary lesions, including central nervous system localisations (CIII).

Conflict of interest statement

Raoul Herbrecht is a member of the advisory board for Pfizer, Merck Sharp Dohme, Schering-Plough, Gilead, Astellas and a member of speakers' bureau of Pfizer, Gilead Sciences, Schering-Plough and Zeneus Pharma and received a research grant from Pfizer.

Ursula Flückiger is a member of the advisory board for Pfizer and Merck Sharp Dohme-Chibret and received unrestricted research grants from AstraZeneca AG, Bristol-Myers Squibb and Wyeth Pharmaceuticals.

Patricia Ribaud is a member of the advisory board for Pfizer and Merck Sharp Dohme.

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Anne Thiebaut and Bertrand Gachot: nothing to declare.

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REFERENCES

1. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;**347**:408–15.
2. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet* 2005;**366**:1435–42.
3. Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clin Infect Dis* 2001;**33**:139–44.
4. Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of haematogenous candidiasis caused by different Candida species. *Clin Infect Dis* 1997;**24**:1122–8.
5. Viscoli C, Girmenia C, Marinus A, et al. Candidaemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). *Clin Infect Dis* 1999;**28**:1071–9.
6. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N Engl J Med* 1991;**325**:1274–7.
7. White MH. The contribution of fluconazole to the changing epidemiology of invasive candidal infections. *Clin Infect Dis* 1997;**24**:1129–30.
8. Ostrosky-Zeichner L, Rex JH, Pappas PG, et al. Antifungal susceptibility survey of 2,000 bloodstream Candida isolates in the United States. *Antimicrob Agents Chemother* 2003;**47**:3149–54.
9. Malani A, Hmoud J, Chiu L, Carver PL, Bielaczyc A, Kauffman CA. *Candida glabrata* fungemia: experience in a tertiary care center. *Clin Infect Dis* 2005;**41**:975–81.
10. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* 1999;**340**:764–71.
11. Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *BMJ* 2001;**322**:579–82.
12. Furrer K, Schaffner A, Vavricka SR, Halter J, Imhof A, Schanz U. Nephrotoxicity of cyclosporine A and amphotericin B-deoxycholate as continuous infusion in allogenic stem cell transplantation. *Swiss Med Wkly* 2002;**132**:316–20.
13. Imhof A, Walter RB, Schaffner A. Continuous infusion of escalated doses of amphotericin B deoxycholate: an open-label observational study. *Clin Infect Dis* 2003;**36**:943–51.
14. Peleg AY, Woods ML. Continuous and 4 h infusion of amphotericin B: a comparative study involving high-risk haematology patients. *J Antimicrob Chemother* 2004;**54**:803–8.
15. Leenders AC, Daenen S, Jansen RL, et al. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. *Br J Haematol* 1998;**103**:205–12.
16. Noskin GA, Pietrelli L, Coffey G, Gurwith M, Liang LJ. Amphotericin B colloidal dispersion for treatment of candidaemia in immunocompromised patients. *Clin Infect Dis* 1998;**26**:461–7.
17. Ito JI, Hooshmand-Rad R. Treatment of Candida infections with amphotericin B lipid complex. *Clin Infect Dis* 2005;**40**(Suppl 6):S384–91.
18. Anaissie EJ, Darouiche RO, Abi-Said D, et al. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. *Clin Infect Dis* 1996;**23**:964–72.
19. Anaissie EJ, Vartivarian SE, Abi-Said D, et al. Fluconazole versus amphotericin B in the treatment of haematogenous candidiasis: a matched cohort study. *Am J Med* 1996;**101**:170–6.
20. Anaissie EJ, Rex JH, Uzun O, Vartivarian S. Predictors of adverse outcome in cancer patients with candidaemia. *Am J Med* 1998;**104**:238–45.
21. Phillips P, Shafran S, Garber G, et al. Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidaemia in non-neutropenic patients. Canadian

Candidaemia Study Group. *Eur J Clin Microbiol Infect Dis* 1997;**16**:337–45.
22. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidaemia in patients without neutropenia. Candidaemia Study Group and the National Institute. *N Engl J Med* 1994;**331**:1325–30.
23. Ostrosky-Zeichner L, Oude Lashof AM, Kullberg BJ, Rex JH. Voriconazole salvage treatment of invasive candidiasis. *Eur J Clin Microbiol Infect Dis* 2003;**22**:651–5.
24. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002;**346**:225–34.
25. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002;**347**:2020–9.
26. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004;**351**:1391–402.
27. DiNubile MJ, Hille D, Sable CA, Kartsonis NA. Invasive candidiasis in cancer patients: observations from a randomized clinical trial. *J Infect* 2005;**50**:443–9.
28. Ruhnke M, Kuse E, Chetchotisakd P, Arns da Cunha C, Diekmann-Berndt H. Comparison of micafungin and liposomal amphotericin B for invasive candidiasis. In: *Proceeding of the 45th interscience conference on antimicrobial agents and chemotherapy*, Washington (DC), December 16–19; 2005 [Abstract M-722c].
29. Reboli A, Rotstein C, Pappas P, Schranz J, Krause D, Walsh T. Anidulafungin vs. fluconazole for treatment of candidaemia and invasive candidiasis. In: *Proceeding of the 45th interscience conference on antimicrobial agents and chemotherapy*, Washington (DC), December 16–19; 2005 [Abstract M718].
30. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004;**38**:161–89.
31. Nucci M, Anaissie E. Should vascular catheters be removed from all patients with candidaemia? An evidence-based review. *Clin Infect Dis* 2002;**34**:591–9.
32. Raad I, Hanna H, Boktour M, et al. Management of central venous catheters in patients with cancer and candidaemia. *Clin Infect Dis* 2004;**38**:1119–27.
33. SFAR, SPILF, SRLF, Société Française d'Hématologie, Société Française de Mycologie Médicale, Société Française de Greffe de Moelle. Management of invasive candidiasis and aspergillosis in adults. *Rev Pneumol Clin* 2004;**60**:289–93.
34. Bohme A, Ruhnke M, Buchheidt D, et al. Treatment of fungal infections in hematology and oncology – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* 2003;**82**(Suppl 2):S133–40.
35. Gavalda J, Ruiz I. Guidelines for the treatment of invasive fungal infection. Invasive fungal infection by Candida spp. Invasive Fungal Infection Study Group (MICOMED) and Infection in Transplantation Study Group (GESITRA) of the Spanish Society for Infectious Diseases and Clinical Microbiology (SEIMC). *Enferm Infecc Microbiol Clin* 2003;**21**:498–508.
36. Hospenthal DR, Murray CK, Rinaldi MG. The role of antifungal susceptibility testing in the therapy of candidiasis. *Diagn Microbiol Infect Dis* 2004;**48**:153–60.
37. Antoniadou A, Torres HA, Lewis RE, et al. Candidaemia in a tertiary care cancer center: in vitro susceptibility and its association with outcome of initial antifungal therapy. *Medicine (Baltimore)* 2003;**82**:309–21.
38. Baddley JW, Patel M, Jones M, Cloud G, Smith AC, Moser SA. Utility of real-time antifungal susceptibility testing for fluconazole in the treatment of candidaemia. *Diagn Microbiol Infect Dis* 2004;**50**:119–24.
39. Lee SC, Fung CP, Huang JS, et al. Clinical correlates of antifungal macrodilution susceptibility test results for non-AIDS patients with severe Candida infections treated with fluconazole. *Antimicrob Agents Chemother* 2000;**44**:2715–8.
40. Nguyen MH, Clancy CJ, Yu VL, et al. Do in vitro susceptibility data predict the microbiologic response to amphotericin B? Results of a prospective study of patients with Candida fungemia. *J Infect Dis* 1998;**177**:425–30.
41. Powderly WG, Kobayashi GS, Herzig GP, Medoff G. Amphotericin B-resistant yeast infection in severely immunocompromised patients. *Am J Med* 1988;**84**: 826–32.
42. Rex JH, Pfaller MA, Barry AL, Nelson PW, Webb CD. Antifungal susceptibility testing of isolates from a randomized, multicenter trial of fluconazole versus amphotericin B as treatment of nonneutropenic patients with candidaemia. NIAID Mycoses Study Group and the Candidaemia Study Group. *Antimicrob Agents Chemother* 1995;**39**:40–4.
43. Wenisch C, Moore CB, Krause R, Presterl E, Pichna P, Denning DW. Antifungal susceptibility testing of fluconazole by flow cytometry correlates with clinical outcome. *J Clin Microbiol* 2001;**39**:2458–62.
44. Clancy CJ, Yu VL, Morris AJ, Snydman DR, Nguyen MH. Fluconazole MIC and the fluconazole dose/MIC ratio correlate with therapeutic response among patients with candidaemia. *Antimicrob Agents Chemother* 2005;**49**:3171–7.
45. Pfaller MA, Diekema DJ, Rex JH, et al. Correlation of MIC with outcome for Candida species tested against voriconazole: analysis and proposal for interpretive breakpoints. *J Clin Microbiol* 2006;**44**:819–26.
46. Abbas J, Bodey GP, Hanna HA, et al. *Candida krusei* fungemia. An escalating serious infection in immunocompromised patients. *Arch Intern Med* 2000;**160**:2659–64.
47. Bodey GP, Mardani M, Hanna HA, et al. The epidemiology of *Candida glabrata* and *Candida albicans* fungemia in immunocompromised patients with cancer. *Am J Med* 2002;**112**:380–5.
48. Safdar A, van Rhee F, Henslee-Downey JP, Singhal S, Mehta J. *Candida glabrata* and *Candida krusei* fungemia after high-risk allogeneic marrow transplantation: no adverse effect of low-dose fluconazole prophylaxis on incidence and outcome. *Bone Marrow Transplant* 2001;**28**:873–8.
49. Bowden R, Chandrasekar P, White MH, et al. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis* 2002;**35**:359–66.
50. Ellis M, Spence D, de Pauw B, et al. An EORTC international multicenter randomized trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. *Clin Infect Dis* 1998;**27**:1406–12.
51. Cornely OA, Maertens J, Bresnik M, Herbrecht R. Liposomal Amphotericin B (L-AMB) as initial therapy for invasive filamentous fungal infections (IFFI): a randomized, prospective trial of a high loading regimen vs. standard dosing (AmBiLoad Trial). *Blood* 2005;**106**. [Abstract 3222].
52. Denning DW, Marinus A, Cohen J, et al. An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. EORTC Invasive Fungal Infections Cooperative Group. *J Infect* 1998;**37**:173–80.
53. Denning DW. Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis* 1996;**23**:608–15.

54. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001;**32**:358–66.
55. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Medicine (Baltimore)* 2000;**79**:250–60.
56. Walsh TJ, Goodman JL, Pappas P, et al. Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with *Aspergillus* species and other filamentous fungi: maximum tolerated dose study. *Antimicrob Agents Chemother* 2001;**45**:3487–96.
57. Cordonnier C, Bresnik M, Ebrahimi R. Liposomal amphotericin B efficacy in invasive filamentous fungal infections: Pooled analysis. In: *Proceeding of the 44th interscience conference on antimicrobial agents and chemotherapy*, Washington (DC), October 30–November 2; 2004 [Abstract M-1022].
58. Wingard JR. Efficacy of amphotericin B lipid complex injection (ABLC) in bone marrow transplant recipients with life-threatening systemic mycoses. *Bone Marrow Transplant* 1997;**19**:343–7.
59. 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.
60. Chandrasekar PH, Ito JI. Amphotericin B lipid complex in the management of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis* 2005;**40**(Suppl 6):S392–400.
61. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clin Infect Dis* 2000;**31**:1155–63.
62. Denning DW, Lee JY, Hostetler JS, et al. NIAID Mycoses study group multicenter trial of oral itraconazole therapy for invasive aspergillosis. *Am J Med* 1994;**97**:135–44.
63. Caillot D, Bassaris H, McGeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. *Clin Infect Dis* 2001;**33**:e83–90.
64. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002;**34**:563–71.
65. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis* 2003;**36**:1122–31.
66. Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood* 2005;**106**:2641–5.
67. Mouas H, Lutsar I, Dupont B, et al. Voriconazole for invasive bone aspergillosis: a worldwide experience of 20 cases. *Clin Infect Dis* 2005;**40**:1141–7.
68. Steinbach WJ, Benjamin Jr DK, Kontoyiannis DP, et al. Infections due to *Aspergillus terreus*: a multicenter retrospective analysis of 83 cases. *Clin Infect Dis* 2004;**39**:192–8.
69. Walsh TJ, Patterson T, Langston A, et al. Posaconazole for treatment of invasive aspergillosis in patients who are refractory to or intolerant of conventional therapy: an externally controlled blinded trial. *Blood* 2003;**102**:195a.
70. Maertens J, Raad I, Petrikkos G, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis* 2004;**39**:1563–71.
71. Kartsonis NA, Saah AJ, Joy LC, Taylor AF, Sable CA. Salvage therapy with caspofungin for invasive aspergillosis: results from the caspofungin compassionate use study. *J Infect* 2005;**50**:196–205.
72. Candoni A, Mestroni R, Damiani D, et al. Caspofungin as first line therapy of pulmonary invasive fungal infections in 32 immunocompromised patients with hematologic malignancies. *Eur J Haematol* 2005;**75**:227–33.
73. Mukherjee PK, Sheehan DJ, Hitchcock CA, Ghannoum MA. Combination treatment of invasive fungal infections. *Clin Microbiol Rev* 2005;**18**:163–94.
74. Aliff TB, Maslak PG, Jurcic JG, et al. Refractory aspergillus pneumonia in patients with acute leukaemia: successful therapy with combination caspofungin and liposomal amphotericin. *Cancer* 2003;**97**:1025–32.
75. Kontoyiannis DP, Hachem R, Lewis RE, et al. Efficacy and toxicity of caspofungin in combination with liposomal amphotericin B as primary or salvage treatment of invasive aspergillosis in patients with hematologic malignancies. *Cancer* 2003;**98**:292–9.
76. Maertens J, Glasmacher A, Herbrecht R et al. Multicenter, noncomparative study of caspofungin combined with other antifungals in adults with invasive aspergillosis refractory or intolerant to prior therapy: final results. In: *Proceeding of the 45th interscience conference on antimicrobial agents and chemotherapy*, Washington (DC), December 16–19; 2005 [Abstract M-954].
77. Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis* 2004;**39**:797–802.
78. Mosquera J, Warn PA, Morrissey J, Moore CB, Gil-Lamaignere DW, Denning DW. Susceptibility testing of *Aspergillus flavus*: inoculum dependence with itraconazole and lack of correlation between susceptibility to amphotericin B in vitro and outcome in vivo. *Antimicrob Agents Chemother* 2001;**45**:1456–62.
79. Johnson EM, Oakley KL, Radford SA, et al. Lack of correlation of in vitro amphotericin B susceptibility testing with outcome in a murine model of *Aspergillus* infection. *J Antimicrob Chemother* 2000;**45**:85–93.
80. Odds FC, Van Gerven F, Espinel-Ingroff A, et al. Evaluation of possible correlations between antifungal susceptibilities of filamentous fungi in vitro and antifungal treatment outcomes in animal infection models. *Antimicrob Agents Chemother* 1998;**42**:282–8.
81. Denning DW, Radford SA, Oakley KL, Hall L, Johnson EM, Warnock DW. Correlation between in-vitro susceptibility testing to itraconazole and in-vivo outcome of *Aspergillus fumigatus* infection. *J Antimicrob Chemother* 1997;**40**:401–14.
82. Lass-Florl C, Kofler G, Kropshofer G, et al. In-vitro testing of susceptibility to amphotericin B is a reliable predictor of clinical outcome in invasive aspergillosis. *J Antimicrob Chemother* 1998;**42**:497–502.
83. Dannaoui E, Borel E, Persat F, Piens MA, Picot S. Amphotericin B resistance of *Aspergillus terreus* in a murine model of disseminated aspergillosis. *J Med Microbiol* 2000;**49**:601–6.
84. Walsh TJ, Petraitis V, Petraitiene R, et al. Experimental pulmonary aspergillosis due to *Aspergillus terreus*: pathogenesis and treatment of an emerging fungal pathogen resistant to amphotericin B. *J Infect Dis* 2003;**188**:305–19.