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.

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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. 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
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>
<thead>
<tr>
<th>Table 1 – Summary of randomised first line therapy trials in invasive candidiasis</th>
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<tr>
<td>Ref.</td>
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<td>22</td>
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<td>21</td>
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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. Neutrophenic 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 study25 including only

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

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Infection</th>
<th>Study design</th>
<th>Antifungal</th>
<th>Total patients</th>
<th>Neutropenic patients with candidaemia</th>
<th>Definition of success</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Candidaemia</td>
<td>Retrospective</td>
<td>Fluconazole or amphotericin B deoxycholate</td>
<td>476&lt;sup&gt;a&lt;/sup&gt;</td>
<td>217&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96 (44%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>Febrile neutropenia</td>
<td>Randomised</td>
<td>Amphotericin deoxycholate Liposomal amphotericin B</td>
<td>344</td>
<td>343</td>
<td>11</td>
</tr>
<tr>
<td>25</td>
<td>Candidaemia</td>
<td>Randomised</td>
<td>Caspofungin</td>
<td>109</td>
<td>109</td>
<td>14</td>
</tr>
<tr>
<td>24</td>
<td>Febrile neutropenia</td>
<td>Randomised</td>
<td>Voriconazole Liposomal amphotericin B</td>
<td>415</td>
<td>422</td>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>26</td>
<td>Febrile neutropenia</td>
<td>Randomised</td>
<td>Caspofungin Liposomal amphotericin B</td>
<td>556</td>
<td>539</td>
<td>12</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number of neutropenic patients belonging to fluconazole or amphotericin deoxycholate group is not stated.

<sup>b</sup> 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 leukemic 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.³³ 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.³⁷-⁴⁶ 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.³⁷,³⁸ 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 leukemic 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 leukemic 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
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. 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 All, 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.

### 3.3. Recommendations

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Overall population</th>
<th>Patients with haematological malignancies and neutropenia</th>
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<tbody>
<tr>
<td>Fluconazole</td>
<td>AI</td>
<td>CIII</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DIII if azole prophylaxis or colonisation with C. glabrata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EIII if colonisation with C. kruzei</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>AI*</td>
<td>CIIIa</td>
</tr>
<tr>
<td>Lipid-amphotericin B</td>
<td>BII</td>
<td>EIII</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>AI</td>
<td>BII</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>AI</td>
<td>BII</td>
</tr>
</tbody>
</table>

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.

caspofungin is the agent of choice for these Candida infections. Although AmB is active against C. glabrata and C. kruzei,
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 (BII). 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 (BII);
- 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). 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.

#### 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. Only data demonstrate convincing superiority in efficacy of liposomal AmB over AmB deoxycholate for the primary treatment of aspergillosis. A pooled analysis of three trials and a compassionate use, multicenter study was performed applying the EORTC-MSG diagnostic criteria for case selection. 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. 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. 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. 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. 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. 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 (%) |
| 1 | Voriconazole | 144 | 53 | 71 | Yes (p = .02) |
| 49 | Amphotericin B deoxycholate | 133 | 32 | 58 | |
| 15 | Amphotericin B colloidal dispersion | 88 | 13 | 40 | No |
| 86 | Amphotericin B deoxycholate | 86 | 15 | 27 | |
| 26 | Liposomal amphotericin B | 26 | 69 | 81 | No |
| 29 | Amphotericin B deoxycholate | 29 | 59 | 62 | |
| 41 | Liposomal amphotericin B (1 mg/kg/d) | 41 | 58* | 41 | No |
| 46 | Liposomal amphotericin B (4 mg/kg/d) | 46 | 54 | 33 | |

a CR + PR + stabilisation.
events than AmB deoxycholate.\textsuperscript{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\textsuperscript{49,51,60,61} (see Tables 6 and 7).

\subsection*{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.\textsuperscript{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%.\textsuperscript{63} Voriconazole was assessed in two open-labelled studies and response rates of 44% and 48% were reported.\textsuperscript{64,65} Superiority of voriconazole over AmB deoxycholate was demonstrated for efficacy, safety and survival in a randomised trial.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{58}

Oral posaconazole has been assessed in salvage therapy of various invasive fungal infections, including a cohort of 107 patients with aspergillosis.\textsuperscript{59} 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.

\subsection*{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.\textsuperscript{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.\textsuperscript{71} Candoni et al. have treated 32 patients, including 8 HSCT recipients, with proven or probable invasive aspergillosis in first-line with caspofungin.\textsuperscript{72} A favourable response was seen in 56% of the patients. Safety profile of caspofungin is excellent with minimal drug-related toxicity.

\subsection*{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{77}

\subsection*{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.\textsuperscript{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.\textsuperscript{81} Lass-Florl et al. correlated susceptibility to AmB and survival in 6 patients.\textsuperscript{82} Twenty two of 23 patients with a resistant strain died. Correlation between failure to AmB and infection with A. terreus has been demonstrated.\textsuperscript{82–84} Data are lacking for the new antifungal agents (see Fig. 2).
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%).

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, 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.

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