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Empirical antifungal therapy in neutropaenic cancer patients with persistent fever ☆

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ABSTRACT

Invasive fungal infections are frequent and severe complications in leukaemic patients with prolonged neutropaenia. Empirical antifungal therapy has become the standard of care in patients with persistent fever despite treatment with broad-spectrum antibiotics. For decades amphotericin B deoxycholate has been the sole option for empirical antifungal therapy. Recently, several new antifungal agents became available. The choice of the most appropriate drug should be guided by efficacy and safety criteria. The recommendations from the First European Conference on Infections in Leukaemia (ECIL-1) on empirical antifungal therapy in neutropaenic cancer patients with persistent fever have been developed by an expert panel after assessment of clinical practices in Europe and evidence-based review of the literature. Many antifungal regimens can now be recommended for empirical therapy in neutropaenic cancer patients. However, persistent fever lacks specificity for initiation of therapy. Development of empirical and pre-emptive strategies using new clinical parameters, laboratory markers and imaging techniques for early diagnosis of invasive mycoses are needed.

1. Introduction

Patients with acute leukaemia and allogeneic haematopoietic stemcell transplant (HSCT) recipients are at high risk of invasive fungal infections (IFI) due to prolonged and profound neutropaenia or immunosuppression for graft-versus-host disease.[1,2] Based on studies conducted in the 1980s, empirical antifungal therapy has become the standard of care in neutropaenic patients in whom fever persists despite treatment with broad-spectrum antibiotics.[3] The rationale for early administration of antifungal agents in these patients include the fact that clinically occult IFI (primarily due to *Candida* or *Aspergillus* species) are a frequent autopsy finding and that persistent fever is often the only early sign of IFI.[4]

For decades amphotericin B (AmB) deoxycholate has been the only option for empirical antifungal therapy. Recently, several new antifungal agents became available. The choice of the most appropriate drug should be guided by efficacy, safety and economic criteria.

The objectives of the present work were to analyse clinical practices in Europe and to propose evidence-based guidelines

☆ 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 No.: LSHC-CT-2004), and International Immunocompromised Host Society (ICHS).

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for empirical antifungal therapy in neutropaenic cancer patients with persistent fever, based on a systematic review of the literature.

2. Methods

2.1. ECIL1 methodology

The common methodology of the ECIL1 working groups has been described in the covering paper.

2.2. Questionnaire on clinical practices in Europe

The questionnaire on clinical practices for the management of infections in neutropaenic cancer patients comprised a section on empirical antifungal therapy for persistent fever. The following items were addressed: use of empirical antifungal therapy for persistent fever, time of initiation of therapy according to clinical presentation, choice of antifungal therapy according to various clinical settings, influence of antifungal prophylaxis on choice of empirical antifungal agents, rationale for current treatment strategies and need for further studies.

2.3. Topics addressed for the guidelines

The following topics were addressed by the working group in a question and answer format:

- Does empirical antifungal therapy reduce the incidence of invasive fungal infection and/or fungal-related mortality?
- Are the antifungal agents used for empirical therapy comparable in terms of efficacy?
- Are antifungal agents used for empirical therapy comparable in terms of adverse events?
- Should different empirical antifungal strategies be used in specific settings (e.g. acute leukaemic patients versus autologous or allogeneic HSCT recipients; the presence of a clinical focus of infection; previous use of antifungal prophylaxis)?

2.4. Literature review and selection of articles

Medline was used to search clinical trials of empirical antifungal therapy published between 1966 and 2005. Medline searches and selections of articles were performed by one of the authors (OM). Medical Subject Heading (MeSH; http://www.nlm.nih.gov/mesh/meshhome.html) terms used in the Medline search were *neutropaenia* or *agranulocytosis*. The Medline search was then narrowed down by using the MeSH terms *antifungal agents* (which was exploded to include all classes and all names of antifungal agents, such as *amphotericin B, fluconazole, itraconazole, voriconazole, caspofungin*), *clinical trials* (which was exploded to include trials phase I-IV, controlled trials, randomised trials, multicentre trials), further limiting the search to *empirical* studies, *human* studies and *English* literature. The MeSH keyword *prophylaxis* was used to exclude studies on antifungal prophylaxis. Additional articles were retrieved from the reference list of articles identified by the Medline search and of guidelines and review articles on the following topics: *empirical antifungal therapy* and *empirical antimicrobial therapy* in neutropaenic cancer patients. Abstracts presented at international meetings (ICAAC, ASH, ECCMID, ASCO, EBMT) between 2002 and 2005 were screened using the following keywords: *neutropaenia* or *agranulocytosis* and *empirical* or *fever* or *antifungal*. Clinical trials were excluded in the presence of one of the following characteristics: (i) patients with documented IFI were studied, (ii) sample size was not based on calculation of the statistical power for testing response to antifungal therapy as primary endpoint, or (iii) sample size was <150 patients if adverse events were the primary endpoint.

2.5. Endpoints

The primary endpoints of this evidence-based review of the literature were the efficacy of and occurrence of adverse events due to empirical antifungal therapy. *Efficacy* was assessed as follows: overall response (composite endpoint including defervescence, response of baseline IFI, absence of breakthrough IFI, no interruption of therapy due to failure or toxicity, survival), resolution of fever, successful treatment of baseline IFI, occurrence of breakthrough IFI, mortality attributed to IFI. *Adverse events* included the following items: nephrotoxicity (defined as a doubling of baseline serum creatinine), infusion-related adverse events and discontinuation of therapy due to adverse events. *Efficacy and adverse events* were also studied in *subgroups* of patients according to underlying conditions (acute leukaemia versus allogeneic or autologous HSCT), documentation of infection (unexplained fever versus clinically documented infection), and use of antifungal prophylaxis.

Quality of evidence and level of recommendation were graded according to the CDC criteria (see the annex of the covering paper).

3. Results

3.1. Questionnaire on clinical practices in Europe

Thirty eight questionnaires were evaluated. Empirical antifungal therapy was considered to be standard practice by a majority of experts (97%). Median time to initiation of antifungal therapy was 5 days (range: 3–8.5 days) for the first febrile episode compared to 3 days (range: 1–8.5 days) for relapsing fever ($p < 0.001$). Half of the experts thought the time of initiation should be delayed in patients with microbiologically documented bacterial infections compared with patients with clinically documented infections or unexplained fever (6.5 days [4–8] versus 4 days [3–6]; $p < 0.001$).

AmB deoxycholate was the most frequently used antifungal agent in patients undergoing induction or consolidation chemotherapy for acute leukaemia or autologous HSCT, while liposomal AmB was the preferred option in allogeneic HSCT recipients (Fig. 1a). The clinical presentation also influenced the choice of the empirical antifungal regimen. AmB deoxycholate was mainly used in patients with unexplained fever. Caspofungin or fluconazole was preferentially used in patients with enterocolitis and/or gastrointestinal *Candida*

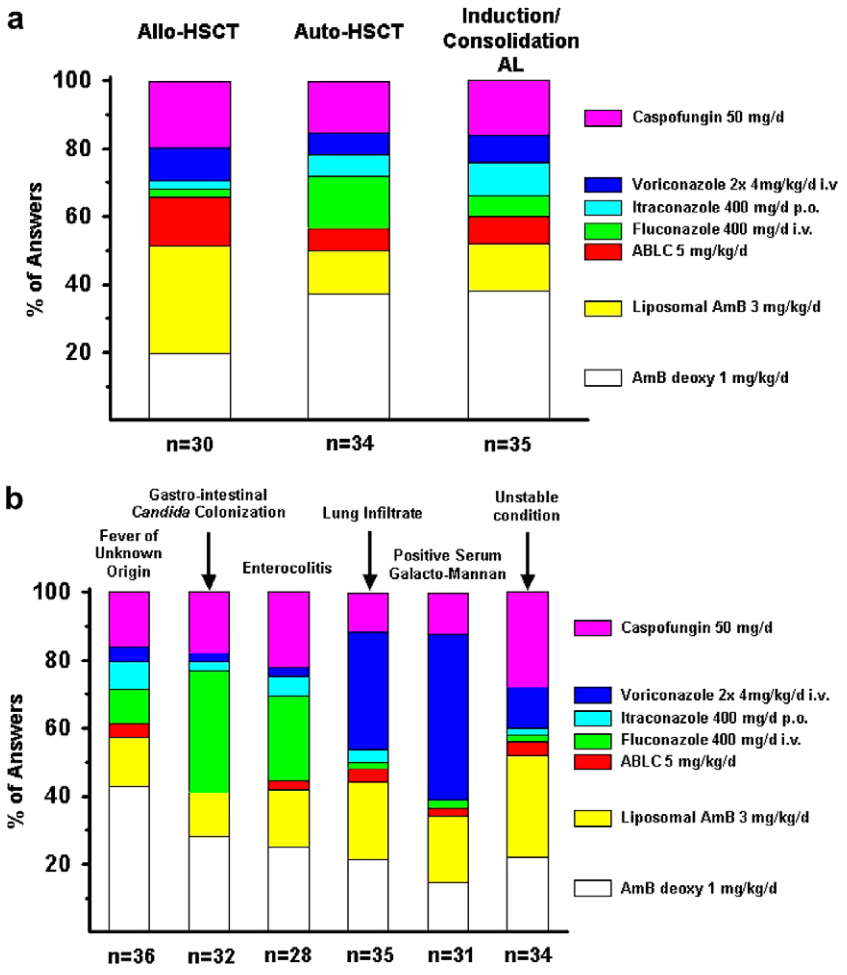

Fig. 1 – Choices of empirical antifungal agents in persistently febrile neutropaenic patients: (a) choice according to the underlying condition; (b) choice according to clinical presentation/condition.

colonisation. Voriconazole was the drug of choice in patients with lung infiltrates and/or a positive serum galactomannan test. Liposomal AmB or caspofungin were preferred in clinically unstable patients (Fig. 1b). The use of antifungal prophylaxis influenced the choice of the empirical antifungal regimen for 62% of experts. Finally, 53% of the experts highlighted the lack of evidence-based guidelines for empirical antifungal therapy and 84% the need for further clinical trials.

3.2. *Literature review*

Twenty five comparative clinical trials of empirical antifungal therapy in neutropaenic cancer patients with persistent fever were included in this analysis (Fig. 2).

3.3. *AmB deoxycholate versus no treatment*

Two open studies conducted in the late 1970s/early 1980s compared empirical AmB deoxycholate 0.5–0.6 mg/kg/d with no treatment in neutropaenic cancer patients with persistent fever despite empirical broad spectrum antibiotic therapy.[5,6] The first trial compared three different strategies in patients with persistent unexplained fever during more than 7 days:

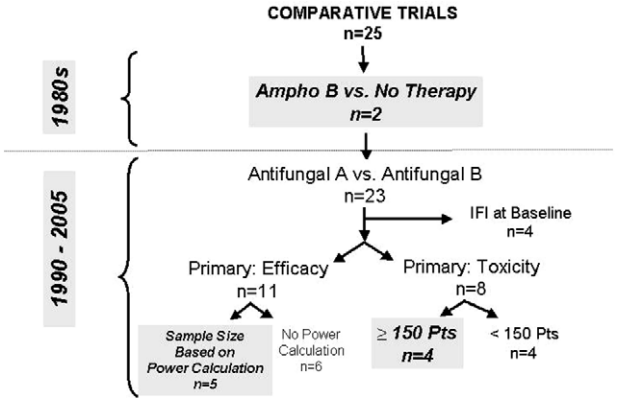

Fig. 2 – Selection of comparative clinical trials on empirical antifungal therapy in persistently febrile neutropaenic cancer patients.

discontinuation of antibiotics ($n = 16$), continuation of antibacterial therapy ($n = 16$) and addition of empirical AmB to antibacterial therapy ($n = 18$). A lower number of IFI and of deaths due to IFI was observed in the group receiving empirical AmB (1/18, 6% [1 *Petriellidium* infection] and

1/18, 6% [1 *Petriellidium* infection], respectively) compared to the group receiving antibacterial therapy alone (4/16, 25% [3 candidiasis, 1 aspergillosis, 1 mixed *Candida* and *Aspergillus* infection] and 3/16 [1 candidiasis, 1 aspergillosis, 1 mixed *Candida* and *Aspergillus* infection], 19%, respectively).[5] The second study conducted by the European Organisation for Research and Treatment of Cancer compared the empirical addition of AmB deoxycholate ($n = 68$) with the continuation of antibacterial therapy alone ($n = 64$) in patients with fever persisting for more than 4 days.[6] Defervescence occurred in 69% (AmB) and 53% (no antifungal therapy) of cases, respectively ($p = 0.09$). IFI occurred in 1/68 (1.5%, 1 invasive candidiasis) and 4/64 (6%, 2 candidiasis, 1 aspergillosis, 1 zygomycosis) patients, respectively (difference not significant). No death due to IFI was reported in the AmB group compared to 4/64 (6%, 2 candidiasis, 1 aspergillosis, 1 zygomycosis) in the control group ($p = 0.05$). The results of these two trials suggested that the empirical use of AmB reduced the occurrence and mortality of IFI. The benefit was primarily observed in patients who were severely neutropaenic, who had not received antifungal prophylaxis with oral polyenes, or who had a clinically documented infection.

These pivotal studies were underpowered to unequivocally prove the efficacy of empirical antifungal therapy for preventing the morbidity and mortality due to IFI. Moreover, these data are probably not entirely representative for the actual patients populations due to evolving cytotoxic and immunosuppressive regimens, changing spectrum of IFI due to the frequent use of systemic antifungal prophylaxis and use of new non-invasive diagnostic tools. Nevertheless, they laid the scientific basis of the present standard of care.[3]

3.4. *Comparison of different antifungal regimens*

Twenty three trials compared the efficacy and safety of various empirical antifungal regimens. Fourteen studies were excluded from the analysis according to our predefined criteria: four included patients with IFI at baseline,[7–10] in six sample size was not based on calculation of the statistical power for testing response to antifungal therapy as primary endpoint,[11–16] and four with toxicity as primary endpoint had included less than 150 patients.[17–20] In the remaining nine trials, AmB was compared either with another form of ampho B ($n = 4$),[21–24] with an azole ($n = 4$),[25–28] or with an echinocandin ($n = 1$)[29] (Table 1). No study compared azoles with echinocandins.

3.5. *Assessment of efficacy*

In seven studies, the *overall response* assessed by a *composite endpoint* based on different combinations of endpoints such as defervescence, successful therapy of baseline IFI, absence of breakthrough IFI, no treatment discontinuation due to failure or toxicity and survival (Table 2A) was similar with the different antifungal regimens (i.e. AmB deoxycholate versus a lipid form of AmB, fluconazole or itraconazole, two different AmB forms, liposomal AmB versus voriconazole or caspofungin).[21–26,29] In one trial, the overall response of itraconazole (63%) was superior to that of AmB deoxycholate (43%, $p = 0.0001$).[27] In one study liposomal AmB was more efficacious (61%) than AmB deoxycholate (32%) for resolution of fever ($p = 0.03$).[21] A recent study failed to demonstrate the non-inferiority (±10%) of voriconazole when compared with liposomal AmB in terms of overall response (difference −5%, 95%CI −11 to 2) or defervescence (difference −4%, 95%CI −10.5 to 2).[28] A secondary analysis using a modified composite endpoint excluding resolution of fever as an endpoint showed equivalent success rates of voriconazole and liposomal AmB: 82 versus 85% (−2%, 95%CI −8 to 2). Two studies reported significant differences in overall survival: 86% with AmB lipid complex versus 97% with liposomal AmB ($p = 0.009$) and 89% with liposomal AmB versus 93% with caspofungin ($p = 0.05$).[24,29]

The clinical usefulness of a primary composite endpoint, whose major driver is the resolution of fever (which is influenced by many factors other than IFI), is a matter of debate. Overall survival is another component of this composite endpoint, which is likely to be influenced by factors other than IFI. Moreover, inclusion of patients with different risk profiles (e.g. differences in haemato-oncological conditions, duration of persistent fever and/or neutropaenia, inclusion of patients with documented bacterial infections and variable use of antifungal prophylaxis), different durations of antifungal therapy and factors such as open design, sample sizes and differences in endpoints for efficacy assessment (e.g. equivalence, non-inferiority, defervescence during or after neutrophils recovery) make the comparison of the study results difficult. It is likely that study design issues played an important role in the failure to demonstrate non-inferiority of voriconazole to liposomal AmB. Paradoxically, these negative results have been influenced mainly by the lower response rates (23% with voriconazole versus 31% with liposomal AmB, $p = 0.04$) reported in patients at low risk of IFI (e.g. autologous HSCT), who failed to defervesce before neutrophil recovery due to a short duration of neutropaenia. Interestingly, a secondary analysis of a large trial showed a similar trend towards a lower success rates of liposomal AmB (31%) versus AmB deoxycholate (37%) in the subgroup of patients with neutropaenia lasting less than 7 days. In conclusion, there was no clear-cut superiority of one antifungal agent over the other ones in these studies.

3.6. *Success of antifungal therapy in patients with IFI at baseline*

This endpoint was reported in four studies.[23,25,28,29] Of note were the higher success rates of caspofungin compared with liposomal AmB for patients with IFI [52% (7/27) versus 26% (14/27), $p = 0.04$], for patients with invasive aspergillosis [8% (1/12) versus 42% (5/12)] and for patients with invasive candidiasis [42% (5/12) versus 67% (8/12)]. This difference resulted in lower mortality due to baseline IFI [11%, (3/27) in the caspofungin group versus 44%, (12/27) in the liposomal AmB group; $p = 0.01$].[29] However, small sample sizes make the interpretation of the results of these subgroups analyses extremely difficult.

3.7. *Occurrence of breakthrough IFI*

This endpoint was analysed in eight studies. In six studies, there were no differences between the experimental and

Table 1 – Synopsis of clinical trials of empirical antifungal therapy in persistently febrile neutropaenic patients

Author, year	Number of Pts	Study design	AF therapy, dose	Primary endpoint	Allo-HSCT	Acute leukaemia	Systemic AF prophylaxis	Days persistent fever at indusion	Days AF therapy
Prentice, 1997[21]	338	Open	L-AmB 1 o r 3 versus AmB-d 1	Severe toxicity	NR	57% 63%	NR	>38 ⩾ 4d	NR
White, 1998[22]	196	Double-blind	ABCD 4 versus AmB-d 0.8	Nephrotoxicity	43% 37%	23% 29%	79% 75%	>38 ⩾ 3d or relapsing	9 7.5
Walsh, 1999[23]	687	Double-blind	L-AmB 0.6 versus AmB-d 0.6	Equivalent efficacy (± 10%)	None	49% 48%	NR	>38 ⩾ 4d	11 10
Wingard 2000[24]	244	Double-blind	L-AmB 3 or 5 versus ABLC 5	Infusion-related toxicity	15% 15%	33% 33%	NR	>38 ⩾ 3d	9–8 7
Winston 2000[25]	317	Open	Fluco 400 versus AmB-d 0.5	Equivalent efficacy (± 15%)	NR	43% 48%	None	>38 ⩾ 3d or relapsing	8 10
Boogaerts 2001[26]	360	Open	Itra 200, then 400 versus AmB-d 0.7–1	Equivalent efficacy (± 15%)	None	64% 62%	35% 40%	>38 ⩾ 3d	8.5 7
Ehninger 2002[27]	162	Open	Itra 200, then 400 versus AmB-d 0.7–1	Severe toxicity	NR	NR	NR	>38 ⩾ 3d	NR
Walsh 2002[28]	837	Open	Vori 6, then 400 versus L-AmB 3	Non-inferior efficacy (± 10%)	18% 19%	53% 51%	53% 59%	>35 ⩾ 4d	7 7
Walsh 2004[29]	1095	Double-blind	Caspo 50 versus L-AmB 3	Non-inferior efficacy (± 10%)	6% 7%	76% 72%	56% 56%	>38 ⩾ 4d or relapsing	11 10

Pts: patients.
AF: antifungal.
NR: not reported.
L-AmB: liposomal AmB, mg/kg/d.
AmB-d: AmB deoxycholate, mg/kg/d.
ABCD: AmB colloidal dispersion, mg/kg/d.
ABLC: AmB lipid complex, mg/kg/d.
Fluco: fluconazole, mg/d.
Itra: itraconazole, mg/d.
Vori: voriconazole, mg/kg/d.
Caspo: caspofungin, mg/d.

Table 2A – Overall response to different empirical antifungal therapies assessed by a composite endpoint including resolution of fever, successful therapy of baseline IFI, absence of breakthrough IFI, no therapy discontinuation and survival

Author, year	Experimental therapy		Control therapy		Statistical analysis
	Drug, dose	Overall response (%)	Drug, dose	Overall response (%)	
Prentice, 1997[21]	L-AmB 1	58	AmB-d 1	49	$P = 0.09$
	L-AmB 3	64			
White, 1998[22]	ABCD 4	50	AmB-d 0.8	43	NS
Walsh, 1999[23]	L-AmB 3	50	AmB-d 0.6	49	NS
Wingard, 2000[24]	ABLC 5	33	L-AmB 3	40	NS
			L-AmB 5	42	
Winston, 2000[25]	Fluco 400	63	AmB-d 0.5	67	NS
Boogaerts, 2001[26]	Itra 200	47	AmB-d 0.7	38	Δ-9 (CI −1 to 13)
Ehninger, 2002[27]	Itra 200	63	AmB-d 0.7	43	$P = 0.0001$
Walsh, 2002[28]	Vori 6	26	L-AmB 3	31	Δ-4 (CI −11 to 2)
Walsh, 2004[29]	Caspo 50	34	L-AmB 3	34	Δ-0 (CI −6 to 6)

NS: not significant.
CI: 95% confidence interval.
L-AmB: liposomal AmB. mg/kg/d.
AmB-d: AmB deoxycholate, mg/kg/d.
ABCD: AmB colloidal dispersion, mg/kg/d.
ABLC: AmB lipid complex, mg/kg/d.
Fluco: fluconazole, mg/d.
Itra: itraconazole, mg/d.
Vori: voriconazole, mg/kg/d.
Caspo: caspofungin, mg/d.

control regimens (Table 2B).[21,22,24–26,29] The study comparing liposomal AmB to AmB deoxycholate reported significantly lower rates of breakthrough IFI with the liposomal form (3% versus 8%, $p = 0.005$).[23] Fewer breakthrough IFI occurred in patients treated with voriconazole than in those treated with liposomal AmB (2% versus 5%, $p = 0.02$).[28]

3.8. *Assessment of response to empirical antifungal therapy in specific subgroups of patients*

The majority of studies did not report data on efficacy of empirical antifungal therapy in specific settings, such as acute leukaemia versus allogeneic or autologous HSCT; or

Table 2B – Breakthrough IFI during empirical antifungal therapy

Author, year	Experimental therapy		Control therapy		Statistical analysis
	Drug, dosing	Breakthrough IFI (%)	Drug, dosing	Breakthrough IFI (%)	
Prentice, 1997[21]	L-AmB 1	3	AmB-d 1	2	NS
	L-AmB 3	2			
White, 1998[22]	ABCD 4	17	AmB-d 0.8	18	NS
Walsh, 1999[23]	L-AmB 3	3	AmB-d 0.6	8	$P = 0.005$
Wingard, 2000[24]	ABLC 5	4	L-AmB 3	4	NS
			L-AmB 5	2	
Winston, 2000[25]	Fluco 400	4	AmB-d 0.5	4	NS
Boogaerts, 2001[26]	Itra 200	3	AmB-d 0.7	3	NS
Walsh, 2002[28]	Vori 6	2	L-AmB 3	5	Δ-3 (C1 1–5), $P = 0.02$
Walsh, 2004[29]	Caspo 50	5	L-AmB 3	5	Δ-1 (Δ-3 to 2)

NS: not significant.
CI: 95% confidence interval.
L-AmB: liposomal AmB, mg/kg/d.
AmB-d: AmB deoxycholate, mg/kg/d.
ABCD: AmB colloidal dispersion, mg/kg/d.
ABLC: AmB lipid complex, mg/kg/d.
Fluco: fluconazole, mg/d.
Itra: itraconazole, mg/d.
Vori: voriconazole, mg/kg/d.
Caspo: caspofungin, mg/d.

unexplained fever versus clinically documented infections; or antifungal prophylaxis versus no antifungal prophylaxis. Wherever available, the data are summarised in the following paragraphs.

3.9. *Efficacy in patients with different risk profiles*

Three studies reported efficacy data in patients with different risk profiles.[26,28,29] Higher overall response rates were described in acute leukaemic patients receiving itraconazole (47%) than in patients receiving AmB deoxycholate (33%, $p = 0.03$), but not in autologous-HSCT recipients (47% versus 48%, respectively).[26] In 'low-risk' patients (i.e. autologous HSCT and acute leukaemia) the overall response to voriconazole was lower (23%) than that of liposomal AmB (31%) ($P = 0.04$).[28] However, no significant difference was observed in 'high-risk' patients (i.e. allogeneic HSCT or relapsing acute leukaemia): 32% versus 36%, respectively. Finally, the overall response was higher in 'high-risk' patients receiving caspofungin (43%) than in patient receiving liposomal AmB (38%, $p = 0.007$). In contrast, there was no difference in 'low-risk' patients (31% versus 32%, respectively).[29]

3.10. *Efficacy according to the aetiology of fever*

Only two studies reported efficacy data according to the aetiology of fever.[6,26] Higher rates of defervescence at day 5 were described in patients with clinically documented infections receiving AmB deoxycholate (76%) than in those without treatment (45%, $p = 0.02$), while no difference between the two regimens was observed in patients with unexplained fever (64% versus 61%).[6] Higher overall response rates were observed in patients with unexplained fever treated with itraconazole (48%) than in those treated with AmB deoxycholate (37%, $p = 0.05$). Response rates to the two regimens were similar in patients with clinically documented infections (37.5% versus 43%, respectively).[26]

3.11. *Efficacy according to the use of antifungal prophylaxis*

Three studies reported the efficacy of empirical therapy in patients who had or had not received antifungal prophylaxis[6,26,29] In patients receiving oral polyenes as antifungal prophylaxis, there was no difference in response to empirical therapy in patients treated with AmB (61%) or no treatment (62%).[6] In contrast, in patients not receiving prophylaxis, defervescence was observed in 78% of cases with empirical AmB versus 45% without empirical antifungal therapy ($p = 0.04$). In patients receiving antifungal prophylaxis (oral polyenes in 2/3 of cases, azoles in the remaining third) empirical itraconazole was successful in 48% of the cases and AmB deoxycholate in 35% of the cases ($p = 0.04$).[26] No difference was observed between the two empirical regimens (45% and 48%, respectively) in patients not receiving antifungal prophylaxis. Finally, response rates of caspofungin and of liposomal AmB were similar in patients with or without systemic antifungal prophylaxis.[29]

In summary, it appears that the results reported by some trials in specific clinical settings are in part conflicting and therefore extremely difficult to interpret. No clear-cut conclusion can be drawn about the effect of either the patients' risk profile, or the presence or absence of a clinical focus of infection at baseline, or on the impact of previous antifungal prophylaxis on the efficacy of different empirical antifungal agents.

3.12. *Adverse events*

3.12.1. *Nephrotoxicity*

In six studies, nephrotoxicity occurred more frequently in patients receiving AmB deoxycholate (range: 24–35%) than in patients receiving the comparator antifungal agent (i.e. lipid form of AmB or azole; range: 1–19%) (Table 3A).[21–23,25–27] Although dosages of AmB deoxycholate (0.5 to 1 mg/kg/d) and liposomal AmB (1 to 5 mg/kg/d) differed among studies, the reported data suggested that the occurrence of nephrotoxicity was not dose dependent. A significantly higher proportion of patients receiving cyclosporine or tacrolimus developed renal toxicity when treated with AmB deoxycholate (68%) compared with AmB lipid complex (8%).[22] Nephrotoxicity occurred more frequently in allogeneic HSCT recipients treated with AmB deoxycholate or liposomal AmB (66% and 33%, respectively) than in patients who had other underlying conditions (34% and 19%, respectively).[23] Nephrotoxicity did not occur more frequently in patients treated with liposomal AmB (8%) than in those treated with voriconazole (7%).[28] Finally, nephrotoxicity occurred more often in patients treated with liposomal AmB (11%) than in those treated with caspofungin (3%).[29]

3.13. *Infusion-related adverse events*

Fever, chills or hypoxia were more frequent in patients receiving AmB deoxycholate (range: 36–57%) than in patients receiving either azoles (2–16%) or liposomal AmB (5–21%).[21–23,25,26] When different forms of AmB were compared, the colloidal dispersion form (80%) resulted in higher rates of adverse reactions than the conventional form (65%) or the lipid complex form (51%) or the liposomal form (21–24%), respectively.[22,24] In the two most recent studies, higher rates of adverse events were reported with liposomal AmB (30–52%) compared with voriconazole (14%) or caspofungin (35%).[28,29] Finally, transient, fully reversible visual adverse events (e.g. altered perception of light) and visual hallucinations occurred more frequently in patients receiving voriconazole than in those receiving liposomal AmB (22% versus 1% and 4% versus 0.5%, respectively).[28]

3.14. *Discontinuation of antifungal therapy due to drug-related toxicity*

Discontinuation of treatment occurred significantly more often in patients receiving AmB deoxycholate (range: 7–57%) than in patients treated with other regimens (range: 1–22%).[21,25–27] Antifungal therapy was also interrupted more frequently in patients receiving AmB lipid complex (32% versus 13% for liposomal AmB),[24] or liposomal AmB (8% versus 5% for caspofungin)[29] (Table 3B).

Compared with the other antifungal agents, AmB deoxycholate was associated with significantly higher rates of

Table 3A – Nephrotoxicity of different empirical antifungal regimens

Author, year	Experimental therapy		Control therapy		P value
	Drug, dosing	Nephrotoxicity (%)	Drug, dosing	Nephrotoxicity (%)	
Prentice, 1997[21]	L-AmB 1	10	AmB-d 1	24	0.01
	L-AmB 3	12			
White, 1998[22]	ABCD 4	8	AmB-d 0.8	35	0.001
	+Cy or Tacro	31	+Cy or Tacro	68	0.001
Walsh, 1999[23]	L-AmB 3	19	AmB-d 0.6	34	0.001
Wingard,2000[24]	ABLC 5	42	L-AmB 3	14	0.001
			L-AmB 5	15	
Winston, 2000[25]	Fluco 400	1	AmB-d 0.5	33	0.001
Boogaerts, 2001[26]	Itra 200	5	AmB-d 0.7	24	0.001
Ehninger, 2002[27]	Itra 200	4	AmB-d 0.7	41	0.001
Walsh, 2002[28]	Vori 6	7	L-AmB 3	8	NS
Walsh, 2004[29]	Caspo 50	3	L-AmB 3	11	0.001

NS: not significant.
Cy: cyclosporin.
Tacro: tacrolimus.
L-AmB: liposomal AmB, mg/kg/d.
AmB-d: AmB deoxycholate, mg/kg/d.
ABCD: AmB colloidal dispersion, mg/kg/d.
ABLC: AmB lipid complex, mg/kg/d.
Fluco: fluconazole, mg/d.
Itra: itraconazole, mg/d.
Vori: voriconazole, mg/kg/d.
Caspo: caspofungin, mg/d.

discontinuation of therapy for adverse events. Albeit less frequent, nephrotoxicity and infusion-related toxicity also occurred in patients treated with lipid forms of AmB, especially in allogeneic HSCT recipients.

4. Recommendations

Is there evidence supporting the use of empirical antifungal therapy in neutropaenic patients with persistent fever to

Table 3B – Discontinuation of empirical antifungal therapy due to adverse events

Author, year	Experimental therapy		Control therapy		P value
	Drug, dosing	Discontinuation due to AE (%)	Drug, dosing	Discontinuation due to AE (%)	
Prentice, 1997[21]	L-AmB 1	8	AmB-d 1	31	0.01
	L-AmB 3	5			
White, 1998[22]	ABCD 4	18	AmB-d 0.8	21	NS
Walsh, 1999[23]	L-AmB 3	NR	AmB-d 0.6	NR	NA
Wingard, 2000[24]	ABLC 5	32	L-AmB 3	13	0.01
			L-AmB 5	12	
Winston, 2000[25]	Fluco 400	1	AmB-d 0.5	7	0.005
Boogaerts, 2001[26]	Itra 200	19	AmB-d 0.7	38	0.001
Ehninger, 2002[27]	Itra 200	22	AmB-d 0.7	57	0.0001
Walsh, 2003[28]	Vori 6	5	L-AmB 3	5	NS
Walsh, 2004[29]	Caspo 50	5	L-AmB 3	8	0.04

NS: not significant.
NR: not reported.
NA: not applicable.
AE: adverse events.
L-AmB: liposomal AmB, mg/kg/d.
AmB-d: AmB deoxycholate, mg/kg/d.
ABCD: AmB colloidal dispersion, mg/kg/d.
ABLC: AmB lipid complex, mg/kg/d.
Fluco: fluconazole, mg/d.
Itra: itraconazole, mg/d.
Vori: voriconazole, mg/kg/d.
Caspo: caspofungin, mg/d.

Table 4 – CDC grading of evidence and recommendation for the empirical use of antifungal agents in neutropaenic patients with persistent fever despite broad spectrum antibiotics

Antifungal agent	Daily dose	CDC Grading		
		Level of recommendation	Evidence for	
			Efficacy	Safety
Liposomal AmB	3 mg/kg	A	|	|
Caspofungin	50 mg	A[a]	|	|
ABLC	5 mg/kg	B	|	|
Voriconazole	2× 3 mg/kg iv	B[a,b,c]	|	|
AmB deoxycholate	0.5–1 mg/kg	B/D[d]	|	|
Itraconazole	200 mg iv	C[a,c]	|	|
Fluconazole	400 mg iv	C[a,c,e]	|	|

a No activity against mucorales.
b Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis and efficacious for prevention of breakthrough IFI.
c Activity against *Candida* may be limited in patients receiving azole prophylaxis.
d B in the absence of/D in the presence of risk factors for renal toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medication including cyclosprin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).
e No activity against *Aspergillus* and other molds. Not approved by the FDA for this indication.

reduce the incidence, the morbidity and/or the mortality of invasive fungal infections?

Yes, Grading: BII.

Comments. The concept of empirical antifungal therapy as standard of care in neutropaenic patients with prolonged fever of undetermined origin is supported by the results of two pioneer, open, not placebo-controlled, randomised studies conducted in the 1980s. However, both trials were underpowered to provide a definitive proof that this approach does reduce the incidence of IFI and IFI-related mortality. Moreover, these results may be not entirely representative of the actual patients populations, due to evolving risk factors, preventive strategies and diagnostic procedures.

Based on efficacy and safety data, is there evidence supporting the use of the following antifungal agents for empirical therapy in neutropaenic patients with persistent fever? (Table 4)

Liposomal AmB: Yes, Grading AI.

Caspofungin: Yes, Grading AI.

AmB lipid complex: Yes, Grading BI.

Voriconazole: Yes, Grading BI.

AmB deoxycholate: Yes, Grading BI (in the absence of risk factors for nephrotoxicity) versus No, DI (in the presence of risk factors for nephrotoxicity).

Itraconazole: Yes, Grading CI.

Fluconazole: Yes, Grading CI.

Comments. Comparative clinical trials performed during the last two decades have not revealed a clear-cut superiority of any antifungal agent over the other ones in terms of efficacy.

Increased occurrence of adverse events, in particular nephrotoxicity in allogeneic HSCT recipients, is the basis for the level B recommendation for AmB lipid complex. Given that it is as active as and substantially less expensive than most other antifungal drugs, a level B recommendation is proposed for AmB deoxycholate (1 mg/kg/d i.v.) provided that risk factors of major toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medications including cyclosporine or tacrolimus in allogeneic HSCT recipients, history of severe toxicity) are absent and that such toxicity does not occur during therapy. Clinicians using this agent must be aware that intolerance may lead to suboptimal dosing and therefore decreased antifungal efficacy. A randomised study compared 4-h with 24-h administration of AmB deoxycholate and reported a reduction of the infusion-related adverse events in the 24-h group (63% versus 20%, $p < 0.001$) and of therapy discontinuations (28% versus 8%, $p = 0.02$).[17] This option may be considered to reduce the infusion-related toxicity of AmB deoxycholate.

Given that it failed the 10% non-inferiority cut-off when compared with liposomal AmB, but that it decreased the occurrence of breakthrough IFI, and because it is the drug of first choice for invasive aspergillosis, voriconazole was given a level B recommendation. Finally, concerns regarding tolerance of itraconazole, emergence of resistant *Candida* species in patients receiving prophylaxis and lack of fluconazole activity against *Aspergillus* species, support a level C recommendation for these azoles.

Voriconazole, itraconazole, fluconazole and caspofungin are inactive against zygomycetes and caution is thus required in patients at high risk for infections due to these emerging molds.

With the exception of the increased nephrotoxicity of AmB in allogeneic HSCT recipients (see comments above), it was not possible to formulate specific recommendations for the choice of antifungal therapy according to the specific underlying conditions, presence of a defined clinical focus of infection, or previous antifungal prophylaxis.

5. Conclusions

Many antifungal regimens can now be recommended for empirical therapy in neutropaenic cancer patients. Initiation of empirical antifungal therapy is triggered by the persistence of fever after 3–7 days of broad spectrum antibiotic therapy. This frequent but non-specific sign of fungal infection does

not take into account recent developments regarding non-invasive diagnosis of IFI using new laboratory markers and imaging techniques. Although the vast majority of European experts use empirical antifungal therapy, current clinical practices are rapidly evolving. Timing of the start of antifungal therapy and choice of the antifungal agent is influenced by a multiplicity of factors, including the patient's risk profile (underlying condition, first versus relapsing episode of fever), whether or not antifungal prophylaxis has been used, clinical presentation, documentation of bacterial infection and results of non-invasive diagnostic tools. Development of new pre-emptive strategies aimed at distinguishing patients who need antifungal therapy from those who do not should be investigated. Initiation of targeted antifungal therapy at an early stage of IFI avoiding unnecessary therapy in patients with non-fungal causes of fever might have a major impact on patients' safety, epidemiology of resistance to antifungals and use of health care resources.[30] Appropriate design including patients' selection, choice of the most suitable antifungal agent and use of relevant endpoints will be key factors for success of future trials.

Conflict of interest statement

Oscar Marchetti has received grants and research supports from Bristol-Myers Squibb, Essex/Schering-Plough, Gilead, Merck Sharp & Dohme-Chibret and Pfizer.

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