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Introduction

This special issue of the European Journal of Cancer deals with an extremely difficult task of providing guidelines and recommendations for the management of infection in leukaemic patients.

Over the last 30 years, the European scientific community has been at the forefront of this area of medicine and has established standards of care. However, infections remain frequent and life threatening particularly in the course of leukaemia. Any attempt to make significant progress in the survival of patients with cancer and mainly haematologic malignancy will rely on optimal complementarity and cooperation of specialists from various disciplines including infectious disease specialists.

The content of this special issue includes the most challenging area of bacterial and fungal infections in leukaemia with useful recommendations for the clinician at the bed side of the patient.

The results of this European initiative also stress the need to address the role of independent clinical research and academic research particularly as many of the infections described are difficult to treat but also to prevent or to diagnose.

However, this series of manuscripts also illustrate that there are still numerous challenges and opportunities ahead for clinical trialists in Europe as numerous questions are still unresolved despite tremendous efforts in the last decades and the significant progress that has been made in the last 10 years.

While the potential market for antiinfectious agents in patients with haematological malignancies is rather limited, there is a clear need for strong partnership between the academic scientific community and the pharmaceutical industry developing new agents as there is not much incentive to develop very expensive drugs in these circumstances.

Major efforts will also be needed to update regularly those recommendations and to improve the methodology of clinical research in infectious disease. Although the control and the management of bacterial infections have been practically solved, this is not the case for invasive fungal infections.

A special issue such as this one should also be useful for health care providers and governments bodies having to allocate funding and reimbursement within limited health care budgets.

European clinical researchers have been pioneers and should pursue their work of international cooperation promoting high quality clinical trials which will be beneficial both for the competitiveness of European research but mainly for all patients with haematological malignancies.

Conflict of interest statement

None declared.

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Editorial

The first European conference on infections in leukaemia: Why and how? ☆

The first European conference on infections in leukaemia (ECIL-1) was organised under the auspices of four groups or society involved in the understanding and management of infectious complications in patients with leukaemia or who have undergone stem cell transplantation: the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT), the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC), the Supportive Care Group of the European LeukaemiaNet (ELN) and the International Immunocompromised Host Society (ICHS). The objective of the Conference was to elaborate guidelines – i.e. recommendations – for the management of bacterial and fungal infections in adult population of high-risk immunocompromised patients. The Conference took place on September 30th–October 1st, 2005 in Juan-les-Pins, France and gathered 59 experts from 24 European countries, Israel and Australia, composed of primarily of haematologists, oncologists, infectious diseases specialists, microbiologists and clinical trials specialists. The manuscripts published in this issue of the Journal present a summary of the main results of the European Consensus Conference and provide guidelines on prophylaxis and treatment of infectious complications occurring in patients with acute leukaemia and recipients of haematological stem cell transplantation.

This meeting has been, in many aspects, a tremendous experience of sharing practices, expert opinions and at the same time, a unique opportunity for intense discussion on the gap that sometimes exists between evidence-based medicine and real life practices. Clinical relevance or applicability is sometimes much more difficult than might have been foreseen. Comprehensive review of the literature on practices that may at first glance not have changed for decades always shed new light on *a priori* or beliefs which after all may not be evidence-based. In this respect, it is always good to challenge dogmas. This kind of exercise also is useful to take a fresh look at issues already broadly discussed in the literature. We are fully aware of the fact that guidelines by definition have rather short life-expectancies. We will update these recommendations at ECIL-2 in September 2007, due to the availability of new data in some of the addressed topics at ECIL1.

1. Methodology of the conference

The Organizing Committee selected a series of topics to be addressed during the Conference. Considering the large number of questions of potential interest in the field, the Organizing Committee elected to limit the spectrum of themes to be covered to the following topics:

Bacterial infections: (1) fluoroquinolone prophylaxis for the prevention of bacterial infections in neutropenic patients, (2) need for aminoglycosides antibiotics as part of the initial empirical antibiotic regimens in febrile neutropenic patients and (3) need for anti-Gram-positive antibiotics for the treatment of suspected Gram-positive infections in febrile neutropenic patients.

Fungal infections: (1) antifungal prophylaxis for the prevention of invasive mycosis, (2) empirical antifungal therapy in patients who remained febrile after broad-spectrum antibiotics therapy and (3) therapy of invasive aspergillosis and of invasive candidiasis.

For each of these six topics, a list of questions and assignments was established as the starting point for discussion by the Working Groups. Each Working Group consisted of 3–6 international experts chosen on the basis of their expertise on the selected topics and who worked under the leadership

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Table 1 – Quality of evidence and Strength of recommendations according to the CDC grading system

Quality of evidence	Strength of recommendations
I Evidence from at least one well-executed randomised trial	A Strong evidence for efficacy and substantial clinical benefit: Strongly recommended
II Evidence from at least one well-designed clinical trial without randomisation; cohort or case-controlled analytic studies (preferably from more than one centre); multiple time-series studies; or dramatic results from uncontrolled experiments	B Strong or moderate evidence for efficacy, but only limited clinical benefit: Generally recommended
III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees	C Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches: Optional
	D Moderate evidence against efficacy or for adverse outcome: Generally not recommended
	E Strong evidence against efficacy or of adverse outcome: Never recommended

of a designated Group leader. The Working Group were formed six months prior to Conference to allow sufficient time for thorough review of the literature and preparation of recommendations.

The Groups were asked to use Medical Subject Heading (MeSH) terms (http://www.nlm.nih.gov/mesh/MBrowser.html) as keywords to search articles published until the date of the conference, in Medline, PubMed or Cochrane databases. Neutropenia was defined as a polymorphonuclear neutrophil (PMN) count <500/mm^3, or <1000/mm^3 expected to drop <500 within 48 h. High risk patients were defined as those expected to have a severe (<100/mm^3) and prolonged (>7 days) neutropenia. Existing guidelines and systematic reviews were also reviewed. Abstracts presented during the period 2002–2005 at annual meetings of the American Society of Hematology, Interscience Conference on Antimicrobial Agents and Chemotherapy, European Society of Clinical Microbiology and Infectious Diseases, American Society of Clinical Oncology, European Group for Blood and Marrow Transplantation were also screened. Articles and abstracts presented or published between September 30 and December 31st, 2005 were not included in the review presented at the conference, but analysed at the initiative of each Working Group, and provisionally graded, pending an update of these guidelines. Analyses focussed primarily on the following end-points: overall survival, cause-specific survival, adverse events, development of antimicrobial resistance and costs whenever this information was available. Quality of evidence and strength of recommendation were graded according to the Centers for Diseases Control grading system (Table 1).

1.1. *Conference, participants and questionnaires*

The participants in the conference were chosen according to their active participation to the EORTC Infectious Diseases Group, the IDWP EBMT, and the ELN group, for their expertise on the topics, and in a balanced representativity of the different European countries in these groups. In order to obtain information about treatment practices in European countries, a questionnaire was developed and mailed to all Conference participants in the summer of 2005. The questionnaire consisted of 8–14 questions per topic, focusing on first or second line strategy, and routine practice. The six topics chosen for the conference were covered. Thirty-eight of the 53 (72%) questionnaires sent to participants not belonging to pharmaceutical companies ($n = 6$) were returned and analysed by Marianne Paesmans, from the EORTC Infectious Diseases Group in Brussels, and we all thank Marianne for her help.

At the meeting, the Working Groups were asked to present an executive summary of the literature review, results of the analyses of the questionnaires and treatment recommendations that were presented in a question and answer format. The recommendations were discussed and critiqued by the Conference participants in plenary session. Treatment recommendations were revised on site by the Working Groups based on the comments made during the plenary session and discussed again in a second plenary session until consensus was reached among participants about quality of evidence and grading of recommendations.

1.2. *Articles*

Each of the articles published in this issue of the *Journal* were written by the Working Groups and reviewed by the one or two chairpersons assigned to this specific part of the plenary session and by members of the Organizing Committee. Modifications were circulated electronically and subsequently agreed upon as part of an iterative process until consensus was reached.

We do hope these guidelines will help the clinician to make rational, evidence-based choices. However, as mentioned in some of these manuscripts, we do not find always the rational for our choices, and need to develop prospective trials each time possible when the answer to an important question is not available in the literature. We also hope to have created, through the ECIL, a new way to share our choices, and recognise our doubts in the management of these patients.

Conflict of interest statement

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Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients ☆

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ABSTRACT

These recommendations have been developed by an expert panel following an evidence-based search of the literature assessing the role of fluoroquinolones in the prevention of bacterial infection in patients with acute leukaemia or bone marrow transplantation and neutropenia. We present results from a questionnaire on the current practice among experts in Europe, show results of the literature search, review recommendations available from other international guidelines and provide the panel's recommendations.

1. Introduction

Several antibiotics have been used for prophylaxis of infections in neutropenic cancer patients.[1] In recent years most of the clinical studies have been conducted with fluoroquinolones. Although the results of randomised controlled trials have suggested that fluoroquinolones might be superior to either placebo, or trimethoprim-sulfamethoxazole or oral

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non-absorbable drugs for the prevention of infections in onco-haematological patients, the evidence provided by these studies was not perceived as entirely convincing.

Before 2005, few studies randomised, placebo-controlled, double-blind trials had been performed and none were large enough to provide conclusive evidence on the benefit of prophylaxis.[2–19] Most of the studies were underpowered to detect a statistically significant effect on mortality and the occurrence of fever requiring empirical antibiotic therapy was either not considered as a study endpoint or was not reduced in a statistically significant manner. Moreover, these studies did not provide clear evidence on the patients who may benefit most from antibiotic prophylaxis. Finally, the use of fluoroquinolone prophylaxis has been questioned, because of reports of increased resistance to this class of antibiotics. All these arguments explain why there was a lack of consensus on the usefulness of fluoroquinolone prophylaxis in patients with neutropenia.[1] We therefore performed a review of the literature to assess the utility of fluoroquinolone prophylaxis in neutropenic acute leukaemia patients. The following questions have been addressed: does fluoroquinolone prophylaxis reduce

(a) the rate of febrile episodes;
(b) the rate of microbiologically documented infections;
(c) the rate of Gram-negative and Gram-positive infections;
(d) all-cause and infection-related mortality.

2. Material and methods

The Cochrane Library (September 2005) and Medline (from January 1980 to September 2005) have been searched. Abstracts presented at the American Society of Haematology (ASH), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the American Society of Clinical Oncology (ASCO) and the European Bone Marrow Transplantation (EBMT) between 2002 and 2005 were also evaluated. References of all included trials and reviews were also scanned. Databases were searched using the terms neutropenia and similar, agranulocytosis and similar, anti-infective agents (including antibacterial and antibiotics), clinical trial and similar, fluoroquinolones or ciprofloxacin, enoxacin, norfloxacin, ofloxacin and pefloxacin. Selection of pertinent articles and abstracts was performed independently by two investigators of the working group, cross-checked and approved by all the members of the study group. Disagreements were resolved by consensus. All randomised, controlled trials performed in neutropenic cancer patients that compared a fluoroquinolone monotherapy versus placebo or no therapy were included in our analysis (Fig. 1). Quality of evidence and levels of recommendations were graded according to CDC methodology.

2.1. *Endpoints*

Selected endpoints were febrile episodes requiring empiric antibiotic therapy, bacterial infections and bacteraemia, Gram-negative infections, Gram-positive infections, and all-cause and infection related mortality. The emergence of resistant bacteria responsible for documented infections following the administration of fluoroquinolone-prophylaxis was also evaluated. Nineteen clinical trials[2–18,20,21] and four meta-analyses[22–25] were identified.

Two large clinical trials[20,21] published in 2005 (the number of patients enrolled in these trials far exceed the total number of patients enrolled in previous studies) and the meta-analysis by Gafter-Gvili et al.[22] were chosen as the main data

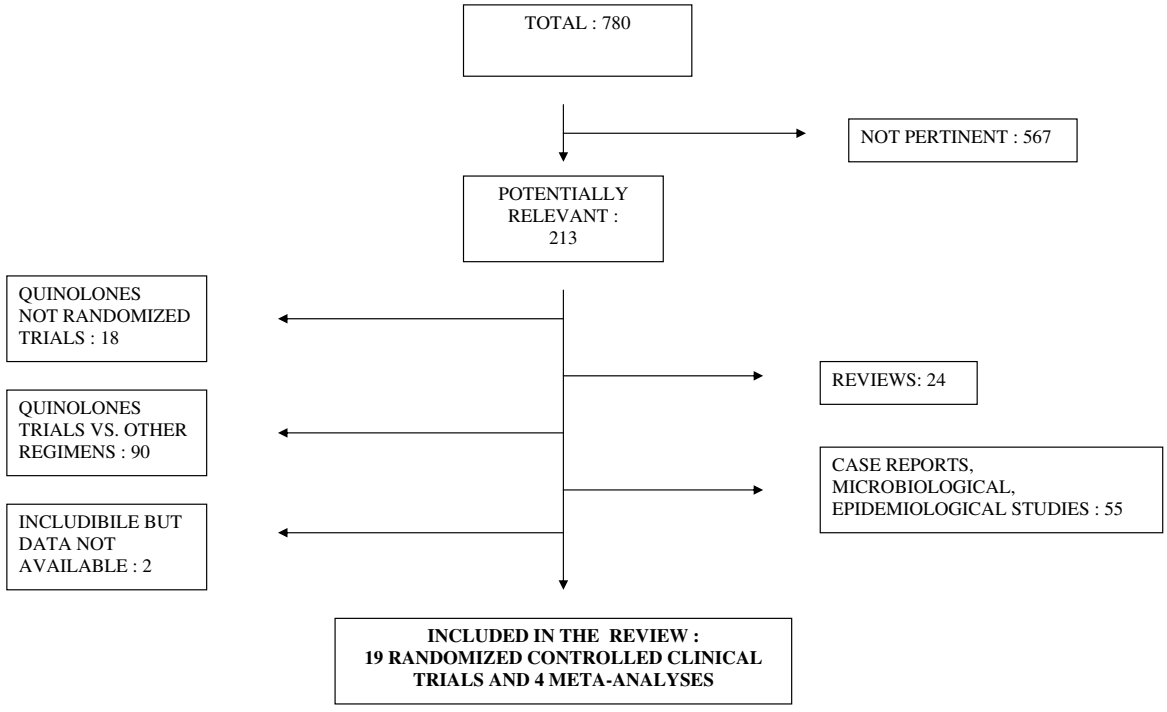

Fig. 1 – Fluoroquinolone prophylaxis: publications identified and exclusions (1980–2005).

sources. This meta-analysis is not only the most recent study on this topic, but it also used all-cause mortality as the main endpoint and included all of the 17 trials performed until 2005 that have compared fluoroquinolones to placebo or no treatment.

3. Results

The characteristics of the studies are shown in Table 1. The majority of these trials included patients with haematological malignancies, most of them with acute leukaemia as the underlying disease. Only five trials were performed in patients with solid tumours or lymphomas. Ciprofloxacin was the fluoroquinolone used in most of the studies, the other fluoroquinolones were norfloxacin, enoxacin, pefloxacin and ofloxacin. Levofloxacin was the agent used in two large, randomised, double-blind, placebo-controlled trials published in 2005. These studies were not included in any of the available meta-analyses.[20,21] The GIMEMA trial[20] was conducted in patients with acute leukaemia or with solid tumour/lymphoma undergoing haematopoietic stem cell transplantation (HSCT).

3.1. *Febrile episodes requiring empiric antibiotic therapy*

As shown in Table 2, the occurrence of febrile episodes requiring the initiation of empiric antibiotic therapy was significantly reduced in patients who had received fluoroquinolone prophylaxis. The meta-analysis of Gafter-Gvili et al.[22] based on 1409 patients (most of whom had haematological malignancies) clearly showed that fluoroquinolone prophylaxis reduced the occurrence of febrile episodes by 33%. The GIMEMA trial[20] reached the same result both in acute leukaemia and in HSCT patients. The number needed to treat to avoid one febrile episode was five in acute leukaemia patients.[21]

3.2. *Bacterial infections*

In acute leukaemia and HSCT patients, microbiologically documented bacterial infections accounted for 30–40% of all febrile episodes (Table 2).[20] Bloodstream infections, which occurred in more than 30% of the patients, were the most frequent cause of documented infections. Fluoroquinolone prophylaxis also reduced the incidence of bacterial infections.

Table 1 – Studies comparing fluoroquinolones to no prophylaxis (1980–2005)

Study (year)	Drug, dose	Total patients	Control	Type of randomised study	Underlyng disease (%)
Sleijfer et al. (1980)	Nalidixic ac. 2 gr qid; TMP-SMZ or Polymyxin	113	No intervention	Not blinded	100 (AL, AA)
Karp et al. (1987)	NOR, 400 mg bid	68	Placebo	Double blinded	100 (AL)
Hartlapp (1987)	OFLO, 200 mg bid	42	No intervention	Not blinded	100 (solid tumours: testicular germ-cell)
Lew et al. (1991)	CIPRO, 750 mg bid	26	Placebo	Double blinded	77 (AL, L, solid tumour); 100 (BMTs)
Sampi et al. (1992)	NOR, 200 mg bid	73	No intervention	Not blinded	90 (AL, solid tumour); 10 autoBMT
Schroeder et al. (1992)	OFLO, 400 mg bid	80	Placebo	Double blinded	2.5 (AL, L, solid tumour)
Maiche et al. (1993)	OFLO, 200 mg bid or CIPRO 750 mg bid	59	No intervention	Not blinded	80 (L, solid tumour: breast)
Talbot et al. (1993)	ENOX, 200 mg bid	119	Placebo	Double blinded	100 (AL)
Yamada et al., (1993)	NOR, 200 mg bid or qid	111	No intervention	Not blinded	100 (AL)
Brodsky et al. (1993)	NOR, 400 mg bid or CIPRO 500 mg bid	25	No intervention	Not blinded	100 (AL)
Carlson et al. (1997)	CIPRO, 500 mg bid	90	No intervention	Not blinded	100 (solid tumour: ovarian cancer)
Casali et al. (1997)	NOR, 400 mg tid	65	No intervention	Not blinded	17 (L, MM, AL)
Thomas et al. 2000	PEFLO, 200 mg qid	160 (3 groups)	Placebo	Double blinded	98 (AL, L, MM, solid tumour); 10 BMT
Tjan-Heijnen et al. (2001)	CIPRO, 750 mg bid and ROXIT, 150 mg bid	163	Placebo	Double blinded	100 (solid tumour: lung cancer)
Nenova et al. (2001)	CIPRO, 500 mg bid[20] PEFLO, ENOX, NOR	70	No intervention	Not blinded	100 (AL, L, MDS CL blast crisis)
Tsutani et al. (2001)	OFLOX, 300 mg bid	22	No intervention	Not blinded	100 (AL, L, MM)
Lee et al. (2002)	CIPRO, 250 mg bid and ROXYT, 150 mg bid	95	No intervention	Not blinded	100 (AL)
Bucaneve et al. (2005)	LEVO, 500 mg/day	760	Placebo	Double blinded	50 (AL), 50 (autologous HSCT)
Cullen et al. (2005)	LEVO, 500 mg/day	1565	Placebo	Double blinded	12 (L) 88 (solid tumour)

AA: aplastic anaemia; AL: acute leukaemia; BMT: bone marrow transplantation; CL: chronic leukaemia; L: lymphoma; MDS: myelodisplastic syndrome; MM: multiple myeloma.

Table 2 – Occurrence of clinically relevant endpoints in a recent randomised controlled trial and a meta-analysis on fluoroquinolone prophylaxis in neutropenic patients

	Fluoroquinolones	Placebo/no treatment	Relative risk (95% CI)	*p*
Febrile episodes				
Gafter-Gvili et al. (2005)	369/798 (46%)	505/701 (72%)	0.67 (0.56–0.81)	<0.001
Bucaneve et al. (2005)	243/375 (65%)	308/363 (85%)	0.76 (0.70–0.83)	0.001
Bacterial infections				
Gafter-Gvili et al. (2005)	171/706 (24%)	318/701 (45%)	0.50 (0.35–0.70)	<0.001
Bucaneve et al. (2005)	74/339 (22%)	131/336 (39%)	0.55 (0.43–0.71)	<0.001
Gram-negative infections				
Gafter-Gvili et al. (2005)	48/588 (8%)	192/588 (33%)	0.39 (0.32–0.46)	0.0001
Bucaneve et al. (2005)	21/339 (6%)	47/336 (14%)	0.44 (0.27–0.72)	0.001
Gram-positive infections				
Gafter-Gvili et al. (2005)	49/588 (8%)	179/588 (30%)	0.42 (0.35–0.50)	0.0001
Bucaneve et al. (2005)	42/339 (12%)	61/336 (18%)	0.68 (0.47–0.98)	0.04
All-cause mortality				
Gafter-Gvili et al. (2005)	33/652 (5.06%)	59/592 (9.9%)	0.52 (0.35–0.77)	0.001
Bucaneve et al. (2005)	10/373 (2.6%)	18/363 (4.9%)	0.54 (0.25–1.164)	N.S.
Leibovici et al. (2006)	41/798 (5%)	56/732 (8%)	0.67 (0.46–0.98)	0.05
Infectious mortality				
Gafter-Gvili et al. (2005)	14/542 (2.5%)	33/480 (6.8%)	0.38 (0.21–0.69)	0.001

All the available meta-analyses have shown a reduction of microbiologically documented infections in patients who have received antibacterial prophylaxis.[22–25] The magnitude of this reduction was about 50% in the meta-analysis by Gafter-Gvili et al. when considering only trials in which fluoroquinolones were used.[22] The results of the GIMEMA study[20] are comparable. In fact, the relative risk reduction was about 50% for patients with either acute leukaemia or HSCT; a significant reduction in the occurrence of bacteraemias was also shown in acute leukaemia and transplanted patients[20] and in the meta-analysis.[22]

3.2.1. *Gram-negative infections*

In acute leukaemia and HSCT patients Gram-negative infections account for about 10% of total febrile episodes. *Escherichia coli* and *Pseudomonas* spp. were the most frequently isolated Gram-negative bacteria (in about 6% and 2% of the total number of febrile episodes, respectively).[20] All of the available meta-analyses performed in neutropenic patients confirmed that antibacterial prophylaxis was associated with a relative risk reduction for Gram-negative infections. It was found to be about 30% in the meta-analysis of Gafter-Gvili et al. when the analysis was limited to fluoroquinolone studies.[22] In both acute leukaemia and HSCT patients,[20] the use of levofloxacin reduced the relative risk of bacteraemia by approximately 70% (Table 2). The effect of fluoroquinolones seemed mainly due to a reduction of *E. coli* infections.[20]

3.2.2. *Gram-positive infections*

In the GIMEMA trial, performed in neutropenic acute leukaemia and HSCT patients, Gram-positive infections accounted for about 15% of the total number of febrile episodes. Staphylococci (76% of coagulase-negative staphylococci) and streptococci were the most frequently isolated Gram-positive bacteria (in about 12% and 3% of total number of febrile episodes, respectively).[20] Among staphylococci, methicillin-resistant strains were predominant. In patients with acute leukaemia or autologous HSTC recipients, the use of levofloxacin was associated with a statistically significant lower rate of Gram-positive infections (relative risk reduction of about 50%) (Table 2). The same trend observed in the subgroup of bloodstream infections was analysed (RR 0.67, 0.45–1.00; $p = 0.06$)[20] (Table 2). As shown in the GIMEMA trial,[20] the effect on Gram-positive infections was mainly due to the reduction of fluoroquinolone-susceptible streptococcal and staphylococcal (primarily *Staphylococcus aureus*) infections. The meta-analysis by Gafter Gvili et al.[22] confirmed these findings (Table 2). Of note, nine of 17 trials examined in the meta-analysis included broad-spectrum fluoroquinolones, such as ciprofloxacin, ofloxacin and pefloxacin. A reduction of Gram-positive infections was also observed in clinical trials in which anti-Gram-positive agents (i.e. beta-lactams, macrolides, rifampin or glycopeptides) were added to the fluoroquinolones. In a systematic review, Cruciani and colleagues[26] found that these antibiotic regimens did not show a clear benefit in terms of morbidity and mortality and were associated with a higher incidence of adverse events. This is the reason why the authors concluded that it was not necessary to add specific anti-Gram-positive coverage to fluoroquinolones.

3.3. *Mortality in neutropenic patients*

None of the fluoroquinolone clinical trials had shown a statistically significant effect of prophylaxis on mortality. The meta-analysis by Gafter-Gvili et al.[22] based on 14 of the 17 clinical trials performed before 2005 and which included a total of 1244 neutropenic cancer patients (with acute leukaemia, solid tumours or who had undergone bone marrow transplantation) showed that fluoroquinolone prophylaxis

significantly reduced all-cause mortality (relative risk reduction of 48%) and infection-related mortality (relative risk reduction of 68%) (Table 2). The reduction of mortality associated with the use of oral antibiotic prophylaxis (i.e. fluoroquinolones and trimethoprim/sulfamethoxazole) was confirmed in the meta-analysis performed by van Wetering et al. (relative risk reduction of 49%) that included 13 trials with a total number of 966 patients.[23] In patients with acute leukaemia and bone marrow transplantation, a meta-analysis performed by Leibovici et al.[27] on 10 randomised trials conducted between 1980 and 2005 that included 1530 patients confirmed that fluoroquinolones reduced all-cause mortality in this subgroup of patients (relative risk 0.67; 95% CI 0.46–0.98). Although not designed to detect a difference in mortality, the GIMEMA trial[20] performed in acute leukaemia/HSCT patients showed that the number of deaths were lower in patients treated with levofloxacin than in those treated with placebo (relative risk 0.54; 95% CI 0.25–1.16) (Table 2).

3.4. *Emergence of resistance*

A major concern of fluoroquinolone prophylaxis is the emergence of resistant bacteria, such as resistant *E. coli*, *Pseudomonas* spp. and methicillin-resistant *S. aureus*.[28–32] The reported rate of emerging resistance differed from study to study according to the type of enrolled population. In the meta-analysis of Gafter-Gvili et al., the incidence of infections caused by fluoroquinolone-resistant bacteria was 5% in patients treated with fluoroquinolones, which was less than in patients treated with TMP-SMZ.[22] In the meta-analysis by Engels et al.,[24] the pooled incidence of quinolone-resistant Gram-negative infections was 3.0% (based on 13 trials) and that of quinolone-resistant Gram-positive infections was 9.4% (based on eight trials). This trend was confirmed in the GIMEMA study[20] with a prevalence of levofloxacin-resistant Gram-positive and Gram-negative infections of 9% and 3%, respectively. Data from several prophylactic studies suggest that the increasing resistance to fluoroquinolones among isolates from onco-haematological patients reflects the pressure exerted by these antibiotics on the endogenous flora, rather than the dissemination of fluoroquinolone-resistant strains in the general population. In fact, fluoroquinolone resistance is a multiclonal, reversible phenomenon.[33,34] Moreover, the pattern of fluoroquinolone resistance did not seem to affect clinical outcomes, such as infection-related morbidity or mortality as shown in the GIMEMA trial.[20] Although there was a high incidence of quinolone-resistant bacterial strains, no deaths occurred in patients with single Gram-negative bacteraemias.

In neutropenic cancer patients, there is no evidence that use of fluoroquinolone prophylaxis was associated with a shift in the type of infections occurring in these patients. The two meta-analyses published in 2005[22,23] do not suggest that fluoroquinolone prophylaxis is associated with a statistically significant increased risk of fungal infections. Finally, fluoroquinolones are not commonly used as empirical antibiotic regimens in high-risk neutropenic patients.[1]

Based on these data, it does not appear that the risk of resistance offsets the favourable impact of fluoroquinolone prophylaxis on mortality, microbiologically documented infections (including both Gram-negative and Gram-positive infections), number of febrile episodes and costs. However, should prophylaxis be adopted, it would seem prudent to carefully monitor the emergence of bacterial resistance (see Section 5).

3.5. *Other endpoints*

A reduction in the use of empiric antibacterial therapy and associated costs was observed in the GIMEMA study.[20]

3.6. *The results of the questionnaire on the European practices concerning antibacterial prophylaxis in neutropenic patients*

Twenty-three of the 38 (61%) clinicians who provided answers to this section of the questionnaire declared they are using antibacterial prophylaxis for the prevention of infections in neutropenic cancer patients. Ciprofloxacin and levofloxacin are the agents most often used. Trimethoprim/sulfamethoxazole is used by a minority of physicians. Among these 23 clinicians, antibacterial prophylaxis is used more often in allogeneic HSCT patients (83%) than in patients with acute leukaemia (69%) or than in recipients of autologous HSCT (61%). Most experts (about 70% in each subgroup) start antibacterial prophylaxis before the onset of neutropenia (i.e. upon hospital admission or when chemotherapy is administered) and continue prophylaxis until the resolution of neutropenia or development of fever and initiation of empirical broad-spectrum antibiotic therapy in which case prophylaxis is discontinued.

3.6.1. *Reasons for using prophylaxis*

As expected, prevention of Gram-negative infections (25%) is the main reason given for using prophylaxis, followed by the prevention of serious infectious complications and bacteraemias. Prevention of fever is in the fourth place, before mortality.

3.6.2. *Evidence from the literature and need for additional studies*

Only six of the 15 physicians not using prophylaxis provided an answer to this question. Five of the them (83%) believed that their choice was supported by data from the literature and only one thought that further studies were needed. Conversely, 15 of the 23 (65%) physicians who are using prophylaxis believed that their choice was supported by data from the literature, but considered that additional studies should be performed.

4. Summary

In high-risk patients, such as those with neutropenia expected to last for more than seven days, comprising primarily patients with acute leukaemia or autologous haematopoietic stem cell transplant (HSCT) recipients, prophylaxis with fluoroquinolones was shown to be effective in reducing (quality of evidence I) (Table 3)

Table 3 – Recommendations for fluoroquinolone prophylaxis for prevention of bacterial infections in neutropenic patients with acute leukaemia or haematopoïetic stem cell transplant

Does fluoroquinolone prophylaxis prevent bacterial infections in patients with acute leukaemia?	Yes Levofloxacin (500 mg once daily): AI Ciprofloxacin (500 mg bid): AI Ofloxacin (200–400 mg bid): BI Norfloxacin (400 mg bid): BI
When should fluoroquinolone prophylaxis be started and how long should it be continued?	Start with chemotherapy and continue until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia (AII)

- All-cause mortality and infection-related mortality.
- Febrile episodes.
- Bacterial infections (including those caused by Gram-negative and Gram-positive bacteria and bloodstream infections caused by Gram-negative bacteria).
- Use of empirical antibiotics.

5. Recommendations (Table 3)

Does fluoroquinolone prophylaxis prevent infections in patients with acute leukaemia or in recipients of haematopoietic stem cell transplantation?

Answer: Yes.

Levofloxacin (500 mg once daily): AI.
Ciprofloxacin (500 mg bid): AI.
Ofloxacin (200–300 mg bid): BI.
Norfloxacin (400 mg bid): BI.

Comments. Ciprofloxacin, norfloxacin and ofloxacin were the most frequently used fluoroquinolones for prophylaxis in randomised clinical trials. Levofloxacin has been used in the two largest randomised trials available today. Given the results obtained in these trials, ciprofloxacin or levofloxacin is the drug of first choice. One randomised trial has demonstrated that ciprofloxacin was superior to norfloxacin.[35] Ofloxacin has a lower *in vitro* activity than ciprofloxacin and levofloxacin against *Pseudomonas* spp. and was found to be less effective than ciprofloxacin in one study.[36] Ofloxacin has been used less often than ciprofloxacin in clinical trials. As shown in Table 1, the dose of levofloxacin was 500 mg given once daily in the two recent clinical trials. In contrast, different daily doses of ciprofloxacin (500–1500 mg/d), ofloxacin (400–800 mg/d) and norfloxacin (400–800 mg/d) have been used in clinical trials. The dose of ciprofloxacin recommended is the one that has been used in most studies. If fluoroquinolone prophylaxis is used for prevention of infections in neutropenic patients, it is recommended to (1) monitor the emergence of fluoroquinolone-resistant bacteria (AIII), and (2) use an empirical antibiotic therapy active against *Pseudomonas* spp. (AIII).

When should fluoroquinolone prophylaxis be started and how long should it be continued?

Answer: Start with chemotherapy and continue until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia (AII).

Comments. As a note of caution, prophylactic administration of ciprofloxacin during cyclophosphamide conditioning is a risk factor for relapse of haematological malignancy in patients undergoing allogeneic bone marrow transplantation. Ciprofloxacin administration prior to cyclophosphamide has resulted in significantly lower exposure of patients with non-Hodgkin lymphoma to 4-hydroxy-cyclophosphamide, the active metabolite of cyclophosphamide.[37–39] Thus antibacterial prophylaxis with fluoroquinolones should be started 24–48 h after the end of high dose cyclophosphamide therapy (AIII).

6. Areas for future studies

Several areas of future clinical investigation deserve consideration, such as placebo-controlled randomised trials in allogeneic HSCT patients and in paediatric cancer patients.

Conflict of interest statement

Giampaolo Bucaneve declares no conflict of interest.

Elio Castagnola has received grant support from Gilead Science and Pfizer Italy and has received fees for lectures from Gilead Science, Pfizer and Merck Sharp and Dohme.

Claudio Viscoli has received grants from Pfizer and Gilead and has been a speaker for Merck, Pfizer, Gilead, Glaxo, Shering-Plough, Bristol-Myers Squibb and Astellas, and participated in advisory boards for Shering-Plough, Pfizer, Gilead and Merck.

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The need for aminoglycosides in combination with β-lactams for high-risk, febrile neutropaenic patients with leukaemia ☆

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ABSTRACT

The efficacy and safety of aminoglycosides given in combination with β-lactams for the treatment of febrile neutropaenia in patients with acute leukaemia or bone marrow transplantation was assessed using an evidence-based review of the literature with the aim to formulate treatment guidelines. These recommendations have been developed by an expert panel of the European Conference on Infections in Leukaemic patients (ECIL-1). We also present results of a questionnaire on current treatment practice in Europe. The expert panel concluded that β-lactam monotherapy is as efficacious as and less toxic than β-lactam-aminoglycoside combination therapy as empirical therapy. The choice of β-lactam should be based on local epidemiological data, antibiotic resistance patterns, recent β-lactam use and available evidence. Combination therapy should be reserved for patients presenting with severe sepsis or septic shock or for those with a high suspicion of resistant Gram-negative infections, pending susceptibility testing and institution of appropriate β-lactam monotherapy.

1. Introduction

Early, broad-spectrum empirical antibiotic treatment for febrile neutropaenic patients has markedly reduced the mortality of Gram-negative infections.[1,2] For about two decades, combinations of an anti-pseudomonal β-lactam antibiotic with an aminoglycoside have been a gold standard for empirical therapy of suspected infections in febrile neutropaenic patients.[3,4] The rationale for combination therapy included broad-spectrum coverage, possible synergistic activity against Gram-negative bacteria (especially *Pseudomonas aeruginosa*) and the prevention of emergence of antibiotic resistance. Since the

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early 1990s, several well-designed, randomised controlled trials have shown that monotherapy with broad-spectrum third- and fourth-generation cephalosporins (ceftazidime, cefpirome and cefepime), carbapenems (imipenem-cilastatin, meropenem) or anti-pseudomonal penicillins combined with an inhibitor of β-lactamases (piperacillin-tazobactam) was as efficacious as and less nephrotoxic or ototoxic than standard β-lactam-aminoglycoside combinations.

Until a few years ago, the management of cancer patients with febrile neutropaenia was fairly uniform. Recent advances in the treatment of cancer and management of chemotherapy-related complications have led to the recognition that all febrile neutropaenic patients are not at the same risk of infectious complications. Several factors can be used to classify patients into low or high risk categories.[5,6] Assessing whether the patient belongs to a low risk or high risk group is important; indeed, while low-risk patients may nowadays be safely treated with oral antibiotics,[7] high-risk patients should continue to receive intravenous broad-spectrum antibiotics. Patients with acute leukaemia, who are the focus of the present guidelines, are generally considered as high-risk patients.

With the advent of broad-spectrum and highly bactericidal β-lactam antibiotics and the shift from Gram-negative bacilli to Gram-positive cocci as the predominant cause of infections in neutropaenic cancer patients in the late 1980s and early 1990s,[8] the need for using an aminoglycoside in the empirical antibiotic regimen was a matter of considerable debate. The objective of the present article was to review the evidence supporting the use of aminoglycosides for managing bacterial infections in febrile neutropaenia. The literature was reviewed with the aim to answer the following questions:

(1) Is β-lactam monotherapy as efficacious as a combination of a β-lactam plus an aminoglycoside for upfront empirical therapy in high-risk febrile neutropaenic patients?
(2) Is a combination of a β-lactam plus an aminoglycoside more nephrotoxic or ototoxic than β-lactam monotherapy?
(3) Is there evidence that once-daily dosing of aminoglycosides is as efficacious as and potentially less toxic than multiple-daily dosing in febrile neutropaenic patients?
(4) Is there evidence supporting the empirical addition of an aminoglycoside to patients initially treated with monotherapy with persistent fever?
(5) Are there specific clinical conditions justifying the use of an aminoglycoside as part of the empirical antibiotic regimen?
(6) Does the use of β-lactam-aminoglycoside combinations in neutropaenic patients prevent the emergence of bacterial resistance?

2. Materials and methods

The Cochrane Library (September 2005) and Medline (January 1980 to September 2005) were used to search articles. Abstracts presented between 2002 and 2005 at annual meetings of the American Society of Haematology (ASH), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the American Society of Clinical Oncology (ASCO) and the European Bone Marrow Transplantation (EBMT) were also evaluated. References of all included trials and reviews were also checked. Databases were searched using the terms 'neutropaenia' or 'agranulocytosis' and similar; 'anti-infective agents' (including antibacterial and antibiotics); 'clinical trial' and similar; and 'aminoglycosides' or 'gentamicin', 'kanamycin', 'amikacin', 'tobramycin' and 'netilmicin'. Selection of relevant articles and abstracts was performed independently by two of the investigators (LD, FM and MP), crosschecked and approved by members of the study group (Fig. 1). Disagreements were resolved by consensus. All randomised controlled trials comparing β-lactam antibiotic monotherapy versus β-lactam–aminoglycoside combination therapy in adult neutropaenic cancer patients with acute leukaemia and meta-analyses comparing these regimens in neutropaenic cancer patients were included in this review. In addition, we included randomised controlled trials and meta-analyses comparing once daily versus multiple daily aminoglycoside dosing schedules in neutropaenic patients. The quality of the evidence and levels of recommendations were graded according to CDC criteria.[9] The endpoints assessed included all-cause mortality, treatment failure as defined in the primary data source, adverse events and infection-related mortality.

3. Results

3.1. *Questionnaire*

The ECIL panel of experts (37 responders) preferred monotherapy for the initial, empirical treatment of febrile neutropaenia (71.2%) and they favour the use of piperacillin/tazobactam (21%), meropenem (16%), imipenem (14.5%), cefepime (13.2 %) and ceftazidime (7%). Less than one-third of responders use β-lactam–aminoglycoside combinations for empirical antibiotic therapy. Twenty-two respondents indicated they would add an aminoglycoside for severe sepsis (29%), suspected *Pseudomonas* infection or resistant Gram-negative infection (26%), secondary infection (10%) and pneumonia (5%). The preferred aminoglycoside for the initial or second-line therapy was amikacin (69%) followed by gentamicin (19%). The duration of aminoglycoside therapy was extremely variable: ranging from 1 to 10–14 days or lasting until recovery of neutropaenia.

4. Review of the literature

4.1. *β-Lactam monotherapy versus β-lactam–aminoglycoside combination therapy*

Seventy-five randomised controlled trials and two meta-analyses comparing β-lactam monotherapy versus β-lactam–aminoglycoside combination therapy for febrile neutropaenia were identified. The two meta-analyses, which included 66

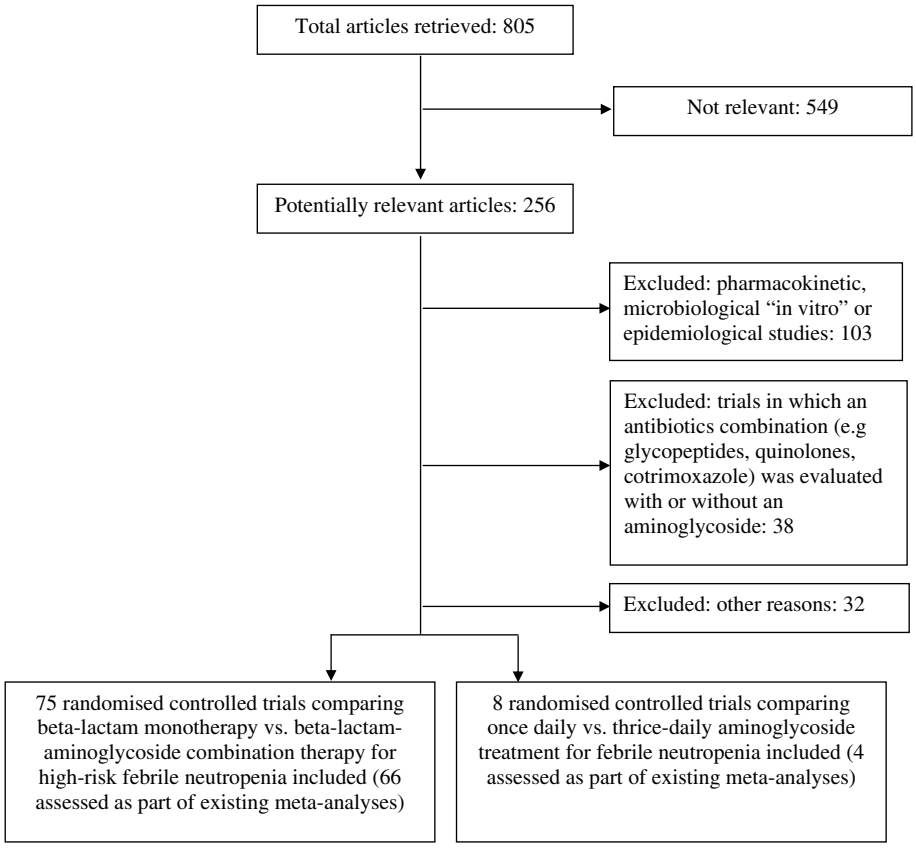

Fig. 1 – Study flow chart.

of the 75 trials identified, served as the main source of data for the present review.[10,11] The remaining nine trials were assessed separately.[12–20] Fifteen further studies, published mainly as abstracts at international meeting, were also evaluated. However, they were not retained in the final analysis for the following reasons: only children included,[21–28] only solid tumour patients included,[29,30] non-randomised trials,[31–34] no comparison between monotherapy and combination therapy[35] and one trial that included both neutropaenic and non-neutropaenic patients.[36]

4.2. *Meta-analysis 1*

The first meta-analysis by Paul et al. was performed as a Cochrane systematic review and published in 2002.[10] Forty-six randomised controlled trials (including 7642 patients) comparing monotherapy with any β-lactam antibiotic to any combination of a β-lactam and an aminoglycoside for the initial empirical treatment of febrile neutropaenic cancer patients were evaluated. The studies were performed between 1981 and 1999. The same β-lactam was used in both study arms in only 9 trials and different β-lactam antibiotics were used in the two study arms in 37 trials, consisting of a broad spectrum β-lactam compared to a narrower-spectrum β-lactam combined with an aminoglycoside. The β-lactams assessed for monotherapy included ceftazidime (14 trials), imipenem (14 trials, including a 2-armed trial), meropenem (6 trials), moxalactam (4 trials), piperacillin/tazobactam (3 trials), cefepime (2 trials) and cefoperazone, ceftriaxone, latamoxef and piperacillin (one trial each). Neutropaenia was defined as a neutrophil count of less than 0.5×10^9/L (500/mm^3) in half of the studies and less than 1.0×10^9/L (1000/mm^3) in the remainder. Bacteraemia was documented in 1874 patients. Microbiologically defined infections due to Gram-negative bacilli accounted for 12% (4–59%) of all treatment episodes and *P. aeruginosa* for less than 2% (0–13%) of episodes.

The study endpoints were analysed overall and in six subgroups: patients with underlying haematological malignancy or bone marrow transplantation, patients with an absolute granulocyte count of less than 0.1×10^9/L (100/mm^3), patients with bacteraemia, patients with microbiologically or clinically defined infections, patients with documented Gram-negative infections and patients with documented *Pseudomonas* infections.

The primary end-point was all-cause mortality defined as death at the end of follow-up for the infectious episode, up to 30 days. It was assessed in 29 studies. The average mortality rate was 6.2% (1.2–30%) with a mortality decline correlating with the year of the study. No significant difference between monotherapy and combination therapy was detected for all cause mortality (including in the six subgroups analysed). The overall relative risk of death was 0.85 (95% confidence interval 0.72–1.02) (favouring monotherapy, Table 1). The same results were obtained when the analysis was performed separately in the trials in which the same β-lactam

Table 1 – Summary of the main results of the two meta-analyses comparing beta-lactam monotherapy to β-lactam-aminoglycoside combination therapy for empirical therapy of febrile neutropaenia

	Paul et al. [10] 47 trials, 7807 patients, 8803 febrile episodes	Furno et al. [11] 29 trials, 4795 febrile episodes
All cause mortality		
•All studies	RR 0.85 CI 0.72–1.02	
•Studies using same β-lactam in both treatment arms	RR 0.73 CI 0.49–1.08	
Infection-related mortality		
•All studies	RR 0.76 CI 0.59–0.98	
•Studies using same β-lactam in both treatment arms	RR 0.72 CI 0.42–1.23	
Treatment failure		
•All studies	RR 0.91 CI 0.85-0.99	OR 0.88 CI 0.78–0.99
•Studies using same β-lactam in both treatment arms	RR 1.12 CI 0.96-1.29	
Bacteraemia	RR 0.69 CI 0.39–1.22 for mortality RR 0.91 CI 0.80–1.04 for failure	OR 0.70 CI 0.54–0.92 for failure
Superinfections	RR 0.97 CI 0.82–1.14 (bacterial superinfections) RR 0.75 CI 0.51–1.09 (fungal superinfections)	
Adverse events[a]	RR 0.57 CI 0.36–0.91	
Nephrotoxicity	RR 0.42 CI 0.32–0.56	

a Adverse events requiring discontinuation of antibiotic treatment. Relative risks (RR) or odds ratios (OR) with 95% confidence intervals (CI) for the comparison of β-lactam monotherapy versus β-lactam-aminoglycoside combination therapy. Values <1 favour monotherapy.

had been used ($n = 5$) or not ($n = 24$) in the two treatment arms (Table 1).

One of the secondary endpoints, treatment failure, was a composite end-point of one or more of the following: death, persistence of infection, recurrence or worsening of clinical signs and symptoms of presenting infection, or any modification of the initial empirical antibiotic treatment. There was no difference between monotherapy and combination therapy with respect to treatment failure in the nine studies (including 2178 episodes of neutropaenia) in which the same β-lactam antibiotic was used in both study arms (relative risk 1.12; 95% CI 0.96–1.29, Table 1), but hetereogeneity was noted between this subset of clinical studies ($P = 0.056$). In contrast, studies comparing different β-lactams provided pooled relative-risk results favouring monotherapy (relative risk 0.86; 95% CI 0.80–0.93, Table 1) without heterogeneity. The same result was observed in the subgroups of patients with microbiologically defined infections and those with haematological malignancies. Infection related mortality was reported in 25 trials, including 5074 patients. Overall results significantly favoured monotherapy (relative risk 0.76; 95% CI 0.59–0.98, $P = 0.03$), with a similar relative risk for studies comparing the same β-lactam and studies comparing different β-lactams (Table 1).

The rate of bacterial superinfections was similar in both groups. Fungal superinfections were more common in the combination treatment group, but the difference did not reach statistical significance. Adverse events occurred significantly less frequently in the monotherapy arm than in the combination treatment arm, especially nephrotoxicity (relative risk 0.42; 95% CI 0.32–0.56), even in the four studies in which once-daily dosing had been used (relative risk 0.20; 95% CI 0.04–0.90). Severe nephrotoxicity, as defined in the studies, was also significantly higher for patients treated with β-lactam–aminoglycoside combination therapy.

4.3. *Meta-analysis 2*

The second meta-analysis by Furno et al. was based on 29 randomised controlled trials comparing monotherapy to combination treatment with an aminoglycoside. A total number of 4795 febrile episodes were analysed of which 1029 were associated with bacteraemia.[11] The primary outcome measure was treatment failure defined as an inadequate clinical response, requiring modification of antibiotic therapy, or resulting in death. In 20 studies, the odds ratios favoured monotherapy and in 8 combination therapy. The pooled odds ratio for clinical failure with monotherapy versus combination therapy was 0.88 (95% CI 0.78–0.99), thus favouring monotherapy (Table 1). However, analysis of higher quality studies and subgroup analyses of patients with severe neutropaenia did not show any significant difference between monotherapy and combination treatment. Analyses of patients more than 14-year-olds and evaluation of bacteraemic episodes showed marginally significant differences favouring monotherapy.

4.4. *Additional studies*

Results of the nine trials that were not included in previous meta-analyses are summarised in Table 2. All-cause mortality was assessed in three trials; their combined results were similar to those obtained in the previous meta-analysis (relative risk 0.80; 95% CI 0.38–1.67). Treatment failure, defined most commonly as lack of defervescence within 72 h or need for antibiotic modification, was assessed in all trials; no significant difference between monotherapy and combination therapy was found in all but one trial comparing piperacillin-tazobactam to ceftriaxone,[18] where monotherapy was advantageous. Other outcomes are detailed in Table 2. Overall, the results were similar to those observed in the previous meta-analyses.

In summary, the review of the literature shows that monotherapy with a broad-spectrum β-lactam

Table 2 – Summary of the main results of randomised controlled trials not included in previous meta-analyses

Study	No. of episodes	Treatment	Patients with AL (%)	All-cause mortality (n/N)	Infection-related mortality (n/N)	Treatment failure (%)	Failure with bacteraemia (n/N)	Super-infections (%)
Bilgir et al. [16]	40	Imipenem versus Piperacillin/ tazobactam + amikacin	Haematological malignancies	NR	NR	M: 35; C: 40	NR	NR
Bru et al. [15]	M: 46 C: 54	Ticarcillin/clavulanate versus Ticarcillin/clavulanate + amikacin	Allogeneic stem cell Tx	NR	NR	M: 17.1; C: 15.5	M: 4/15; C: 1/13	M: 6.5; C: 13
Gaytan-Martinez et al. [17]	M: 63; C: 54	Cefepime versus ceftazidime + amikacin	AL+NHL	NR	NR	M: 14.2; C: 12.9	NR	NR
Gorschluter et al. [18]	M: 98; C: 85	Piperacillin/tazobactam versus Ceftriaxone + gentamicin	M: 85.7; C: 82.4	M: 5/98; C: 8/85	M: 4/98; C: 6/85	M: 42.9; C: 64.7[a]	M: 14/24; C: 19/25	NR
Kiel et al. [14]	M: 35; C: 35	Piperacillin/tazobactam versus Piperacillin/tazobactam + netilmicin	All	NR	NR	M: 40; C: 33	NR	NR
Kliasova et al. [13]	M: 23 C: 20	Meropenem versus Ceftazidime + amikacin	Bone marrow Tx	M: 1/22; C: 2/20	NR	M: 35; C: 50	NR	NR
Miller et al. [19]	M: 45; C: 41	Imipenem versus Piperacillin + tobramicin	NR	NR	NR	M: 10; C: 24	NR	M: 18; C: 7
Tamura et al. [20]	M: 95; C: 94	Cefepime versus Cefepime + amikacin	M: 47.4; C: 47.9	M: 7/95; C: 5/94	NR	M: 67.4; C: 56.3	M: 3/4; C: 4/7	NR
Wrzesien-Kus et al. [12]	M: 19 C: 21	Cefepime versus Cefepime + amikacin	NR	NR	NR	M: 52.6; C: 47.6	NR	NR

M: monotherapy; C: combination therapy; NR: not reported; AL: acute leukaemia; NHL: non-Hodgkin's lymphoma; Tx: transplantation.
a Significant advantage to monotherapy, $P = 0.0047$; no significant difference between monotherapy and combination therapy for all other comparisons.

antibiotic is as efficacious as and less toxic (especially nephrotoxic) than combination therapy with a β-lactam and an aminoglycoside.

4.5. *Once daily versus multiple daily dosing of aminoglycosides*

Eight randomised controlled trials compared the efficacy and safety of once versus thrice daily aminoglycoside therapy in febrile neutropaenic patients.[37–44] Four of these trials have been evaluated in a previous meta-analysis.[45] Clinical failure and mortality rates were similar in patients treated with once daily or thrice daily aminoglycosides (risk ratio 0.97; 95% CI 0.91–1.05 for clinical failure and 0.93; 95% CI 0.62–1.41 for mortality). The pooled nephrotoxicity risk ratio was somewhat lower in once-daily regimens than in multiple daily regimens (0.78; 95% CI 0.31–1.94), but did not reach statistical significance. Two additional studies compared single daily amikacin with ceftriaxone versus thrice daily amikacin with ceftazidime and showed similar efficacy and toxicity rates.[38,39] Sung et al. compared once versus thrice daily tobramycin combined with either piperacillin or ceftazidime. A statistically significant higher efficacy and a trend towards lower nephrotoxicity were noted in the once-daily regimen.[37] Torfoss et al. compared tobramycin given once versus three times a day in combination with penicillin for febrile patients with acute leukaemia or lymphoma and severe neutropaenia.[43] Efficacy and toxicity rates were similar in the aminoglycoside treatment groups.

In summary, the evidence gathered in several randomised controlled trials indicates that once daily dosing of an aminoglycoside is as efficacious as and probably less nephrotoxic than multiple daily dosing among neutropaenic patients. Similar results have been obtained in multiple randomised trials and several meta-analyses conducted in non-neutropaenic patients.[46–52]

4.6. *Recommendations for aminoglycosides in international guidelines*

Recent guidelines on the use of antimicrobial agents for the management of febrile neutropaenia have also addressed the issue of the use of aminoglycosides. In the guidelines of the Infectious Diseases Society of America (2002), β-lactam monotherapy (cefepime, ceftazidime, imipenem, meropenem and possibly piperacillin-tazobactam) was considered equivalent to combination therapy for empirical therapy of uncomplicated episodes of febrile neutropaenia.[9] In the case of progression of infection or development of a complication, the guidelines suggested that consideration be given to addition of an appropriate antibiotic or a change to different antibiotics. There was no specific recommendation regarding aminoglycoside-dosing schedule.

The guidelines of the Infectious Diseases Working Party of the German Society of Haematology and Oncology (2003) listed monotherapy (ceftazidime, cefepime, imipenem/cilastatin, meropenem and piperacillin-tazobactam) and combination therapy (acylaminopenicillin or third- or fourth-generation cephalosporins plus an aminoglycoside) as equivalent options for first-line treatment.[53] In case of persistence of fever and neutropaenia 6–9 days after initial antibiotic therapy, once or thrice-daily administration of amikacin and netilmicin was recommended as a treatment option in patients at intermediate risk who had been initially treated with monotherapy.

In the guidelines of the National Comprehensive Cancer Network (2005), broad-spectrum monotherapy was considered comparable to β-lactam aminoglycoside combination therapy. However, treatment with an anti-pseudomonal β-lactam with an aminoglycoside was recommended as first line therapy in clinically unstable patients (e.g. hypotension) or in patients at high-risk for *P. aeruginosa* infection.[54] The guidelines also recommend that the addition of an aminoglycoside to the initial antibiotic regimen be considered for patients with persistent fever, those who are clinically unstable and for microbiologically defined *P. aeruginosa* infections. There was no recommendation for the use of once-daily dosing of aminoglycosides.

5. Recommendations

The recommendations are summarised in Table 3 and are detailed below.

(1) Is β-lactam monotherapy as efficacious as a combination of a β-lactam plus an aminoglycoside for upfront empirical therapy in high-risk febrile neutropaenic patients with acute leukaemia or HSCT?

Answer: Yes, grading AI.

Comments: Available evidence shows that monotherapy is at least as efficacious as β-lactam-aminoglycoside combination therapy with regard to overall survival, overall response defined as a resolution of fever or of infection without modification of the initial antibiotic regimen, response of documented Gram-negative infections, and infection-related mortality. The monotherapies evaluated in these trials included ceftazidime, cefepime, imipenem/cilastatin, meropenem and piperacillin/tazobactam. Local advantages and disadvantages to each of the monotherapies may influence selection of the specific monotherapy. Ceftazidime may be inadequate in settings with high prevalence of extended spectrum β-lactamases producing microorganisms and is less active against Gram-positive bacteria;[55] imipenem has been associated with increased rates of pseudomembranous colitis;[56,57] piperacillin-tazobactam is associated with false-positive galactomannan assays;[58] and cefepime was associated with higher all-cause mortality when compared to other monotherapies in randomised trials.[56] Thus, the appropriate β-lactam for monotherapy should be selected according to local epidemiology, antibiotic resistance patterns, recent β-lactam use and available evidence.

(2) Is a combination of a β-lactam plus an aminoglycoside more nephrotoxic or ototoxic than β-lactam monotherapy?

Answer: Yes, grading AI for both nephrotoxicity and ototoxicity.

Table 3 – Summary of recommendations

Problem	Recommendation	Grading[a]
BL monotherapy is as efficacious as BL + AG as empirical therapy of febrile neutropaenia	Yes	A I
BL + AG combination is more nephrotoxic and ototoxic than BL monotherapy	Yes	A I
OD dosing of AG are as efficacious as and less nephrotoxic than MDD	Yes	A I
Empirical addition of AG to the initial regimen in patients with persistent fever	No	C III
Empirical use of BL + AG combination in patients in whom a resistant Gram-negative infection[b] is suspected	Yes	C III
Addition of AG to the initial regimen in case of documented *P. aeruginosa* infection	No	C III
Use of BL + AG combination in patients with severe sepsis or septic shock	Yes	C III
Use of BL + AG in neutropaenic patients with pneumonia	No	C III
Use of BL + AG combination to prevent emergence of resistance during therapy	No	B I

BL: β-lactam; AG: aminoglycoside; OD: once-daily dosing; MDD: multiple-daily dosing.
a Level of evidence and level of recommendation.[9]
b Local epidemiology and previous antibiotic treatments should be taken into account.

Comments: Nephrotoxicity was evaluated in several trials comparing monotherapy with combination therapy. Amikacin, netilmicin, gentamicin and tobramycin were the aminoglycosides used in these trials. Nephrotoxicity and severe nephrotoxicity occurred significantly more often among patients treated with combination therapy than in those treated with monotherapy. The number needed to prevent one episode of nephrotoxicity when using β-lactam monotherapy was 31.[10] Among 14 trials reporting ototoxicity, 19 patients developed ototoxicity in the combination treatment arm versus three patients in the monotherapy arm (unpublished data from Paul et al.[10]). Routine monitoring for ototoxicity with audiometry was rarely performed in these studies.

(3) Is there evidence that once-daily administration of aminoglycosides is as efficacious as and potentially less toxic than multiple-dose administration for febrile neutropaenic patients?

Answer: Yes, grading AI.

Comments: Results from several randomised controlled trials suggest that survival rates and efficacy (as assessed by successful treatment without the need for modification of antibiotic therapy) are similar for high-risk neutropaenic patients treated with either once daily or multiple dose administration of aminoglycosides. Moreover, nephrotoxicity was less frequent among patients treated with once-daily dosing.

(4) Is there evidence supporting the empirical addition of an aminoglycoside to patients initially treated with monotherapy with persistent fever?

Answer: No, grading CIII.

Comments: We are not aware of clinical trials that have addressed that question for patients with persistent fever.

(5) Are there specific clinical conditions justifying the use of an aminoglycoside as part of the empirical antibiotic regimen? Specific clinical conditions for which the use of an aminoglycoside might be considered include a high suspicion or microbiological documentation of an infection caused by *P. aeruginosa* or resistant Gram-negative bacilli, pneumonia and the occurrence of life-threatening conditions, such as severe sepsis or septic shock. We will consider each of these possible indications below.

(a) Suspicion of infections caused by resistant *P. aeruginosa* or other resistant Gram-negative bacteria.

Answer: Yes, grading CIII.

Comments: There are no data to support the empirical use of a combination of an aminoglycoside and a β-lactam antibiotic for treating infections suspected to be due to resistant Gram-negative bacilli (including *P. aeruginosa*). However, given the risk of poor outcome in neutropaenic patients treated with inappropriate antibiotics, especially in centres where resistant Gram-negative bacteria are a concern, we recommend using a combination therapy as empirical regimen until microbiological data become available. The aminoglycoside should be discontinued as soon as resistance to the β-lactam antibiotic has been ruled out.

(b) Documented *Pseudomonas aeruginosa* infections

Answer: No, grading CIII.

Comments: In the meta-analysis by Paul et al. no significant differences were observed between monotherapy and combination therapy with respect to the subgroup of patients with documented *P. aeruginosa* infections.[10] Only 58 patients were assessed for mortality and 139 patients for treatment failure. In a meta-analysis including non-neutropaenic patients, a significant survival benefit for combination therapy was found in the subgroup of patients with *P. aeruginosa* bacteraemia.[59] However, this meta-analysis included observational studies, a heterogenous patient population and single aminoglycoside treatment in the monotherapy arm, precluding firm conclusion regarding β-lactam monotherapy. Thus, there is no proven advantage of adding an

aminoglycoside to a β-lactam antibiotic when the *P. aeruginosa* is fully susceptible to the β-lactam agent. In fact, susceptibility of gram-negative bacilli to the β-lactam used is a primary determinant of outcome.[60]

(c) Severe sepsis and septic shock.

Answer: Yes, grading CIII.

Comments: Severe sepsis and septic shock occur in only 1–2% of febrile neutropaenic episodes.[61,62] However, given that patients with septic shock often are excluded from many clinical studies, the incidence of these complications might be underestimated. In a logistic regression analysis of patient's outcome performed in 909 neutropaenic cancer patients with bacteraemia, the risk of death was significantly increased in hypotensive patients.[63] Although no data are available, it is recommended to use an aminoglycoside antibiotic in febrile neutropaenic patients with severe sepsis or septic shock.

(d) Pneumonia.

Answer: No, grading CIII.

(6) Does the use of β-lactam-aminoglycoside combinations in neutropaenic patients prevent the emergence of resistant bacteria?

Answer: No, grading BI.

Comments: Current evidence indicates that β-lactam monotherapy is not associated with an increased risk of emergence of resistant bacteria when compared with β-lactam and aminoglycoside combinations. Paul et al. assessed bacterial superinfections as a surrogate marker of induction of resistance. No difference was found between combination and monotherapy.[10] Only two studies compared the frequency of colonisation with resistant Gram-negative bacteria after treatment, which occurred in 5 of 152 patients (3%) treated with monotherapy and in 1 of 152 patients (0.6%) treated with a combination of antibiotics.[64,65] Bliziotis et al. conducted a meta-analysis of randomised controlled trials aimed at comparing the effect of combinations of an aminoglycoside and a β-lactam antibiotic and of β-lactam monotherapy on the emergence of antimicrobial resistance among non-neutropaenic patients.[66] Beta-lactam monotherapy was associated with fewer superinfections, while treatment failure attributable to resistance induction or superinfections did not differ significantly between the two study arms. Thus, data from randomised trials do not suggest that the use of an aminoglycoside-containing antibiotic regimen is associated with a reduced risk of the emergence of resistant bacteria.

Conflict of interest statement

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Empirical use of anti-Gram-positive antibiotics in febrile neutropaenic cancer patients with acute leukaemia ☆

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ABSTRACT

Gram-positive infections including those due to methicillin-resistant staphylococci occur frequently in febrile neutropaenic patients. Although few data support the empirical addition of a glycopeptide antibiotic to the standard broad-spectrum antibiotic regimen, these agents are often used in many cancer centres. The emergence of infections due to vancomycin-resistant enterococci and glycopeptide-intermediate staphylococci has led to recommendations for a restricted use of glycopeptide antibiotics. The objective of the present work was to formulate evidence-based guidelines for the empirical use of anti-Gram-positive antibiotics in neutropaenic patients with acute leukaemia.

1. Introduction

Early empirical administration of broad spectrum antibiotics has been shown to decrease the mortality due to bacterial infections in febrile granulocytopenic cancer patients.[1] Anti-pseudomonal beta-lactams with or without an aminoglycoside are standard antibiotic regimens for the initial therapy of febrile neutropenia in patients with haematological malignancies, i.e. with severe and prolonged neutropenia.[2,3]

Several studies performed in adults and pediatric neutropaenic patients have shown a shift towards an increased proportion of infections caused by Gram-positive bacteria. Indeed, single Gram-positive bacteraemias accounted for 30% of single organism bacteraemias before 1985 and increased to 60–70% in the 1990s.[4] With the increase in documented Gram-positive infections in febrile neutropaenic patients, including those due to methicillin-resistant staphylococci, the addition of a glycopeptide antibiotic to the standard regimen became controversial.[2] Over the last 10 years, the emergence of infections due to vancomycin-resistant enterococci and glycopeptide-intermediate staphylococci has led to recommendations to restrict the use of glycopeptide antibiotics.[5] The objective of the present work was to formulate evidence-based guidelines for the use of anti-Gram-positive antibiotics in neutropaenic patients with acute leukaemia.

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2. Materials and methods

2.1. Issues addressed in the guidelines

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

(1) Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated for upfront empirical therapy of febrile neutropenia in patients with acute leukaemia?
(2) Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated for persistent fever in neutropaenic patients with acute leukaemia?
(3) Are there specific indications justifying the upfront use of anti-Gram-positive antibiotics as part of the empirical therapy?

2.2. Data source and review process

Medline was used to search articles published between 1st January 1966 and 1st September 2005. Medline searches and selections of articles were performed by one of the authors (O.M.). Medical Subject Heading (MeSH; http://www.nlm.nih.gov/mesh/meshhome.html) terms used in the Medline search included *leukaemia*, *neutropenia* and *agranulocytosis*. The Medline search was then narrowed by using the MeSH terms *anti-infective agents* (which was exploded to include glycopeptides such as vancomycin and teicoplanin, oxazolidinones such as linezolid and streptogramins such as quinupristin/dalfopristin), *clinical trials*, further limiting the search to human studies and English literature. Additional articles were retrieved from references of articles identified by the Medline search and of meta-analyses, guidelines and review articles on *antimicrobial agents in febrile neutropaenic patients*. Abstracts presented between 2002 and 2005 at international meetings of the American Society of Hematology (ASH), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the American Society of Clinical Oncology (ASCO) and the European Bone Marrow Transplantation (EBMT) were screened using the following keywords: *neutropenia*, *agranulocytosis*, *empirical treatment*, *glycopeptides*, *oxazolidinones* and *streptogramins*.

2.3. Literature review and selection of articles

A study was considered eligible provided it was a randomised, controlled trial assessing the role of glycopeptides, oxazolidinones or streptogramins antibiotics given in addition to broad spectrum antibiotics for patients with acute leukaemia and febrile neutropenia. Abstracts and articles fulfilling the selection criteria were reviewed to exclude studies that were not relevant for the three issues addressed in the present guidelines (see the corresponding section). Exclusion criteria were (i) trials comparing two different glycopeptides without a placebo group, (ii) trials comparing two anti-Gram-positive antibacterial agents without a placebo group, (iii) trials comparing two different broad spectrum antibiotic regimens combined with the same glycopeptide, (iv) duplicate publications and (v) non-comparative studies. Meta-analyses assessing the role of glycopeptides in neutropaenic patients were also included. Articles were chosen by two independent reviewers (A.C. and O.M.) and reviewed until consensus was reached between the three authors about the selection of articles.

2.4. Data extraction and endpoints

The following data were extracted from each study: patient characteristics, underlying haematological disease, antimicrobial agent and doses used. The primary endpoints were the efficacy and safety of the empirical addition of anti-Gram-positive antibiotics to broad spectrum antibiotics.

Efficacy was assessed in terms of overall mortality and mortality related to infection, success rates without or with modification of empirical antimicrobial therapy, time to defervescence, breakthrough infections. Success without modification of the allocated regimen was defined as resolution of fever and clinical signs of infection, eradication of any infecting microorganism, absence of clinical deterioration, absence of breakthrough infection and survival during therapy. The following *adverse drug reactions* were analysed: *nephrotoxicity*, which was defined as a rise in serum creatinine (increase of more than 0.45 μmol/l or a two-fold increase over baseline) or a decrease of creatinine clearance (more than 50% from baseline value) and *skin rashes*.

Quality of evidence and level of recommendation were graded according to the CDC criteria.

2.5. Questionnaire on clinical practices in Europe

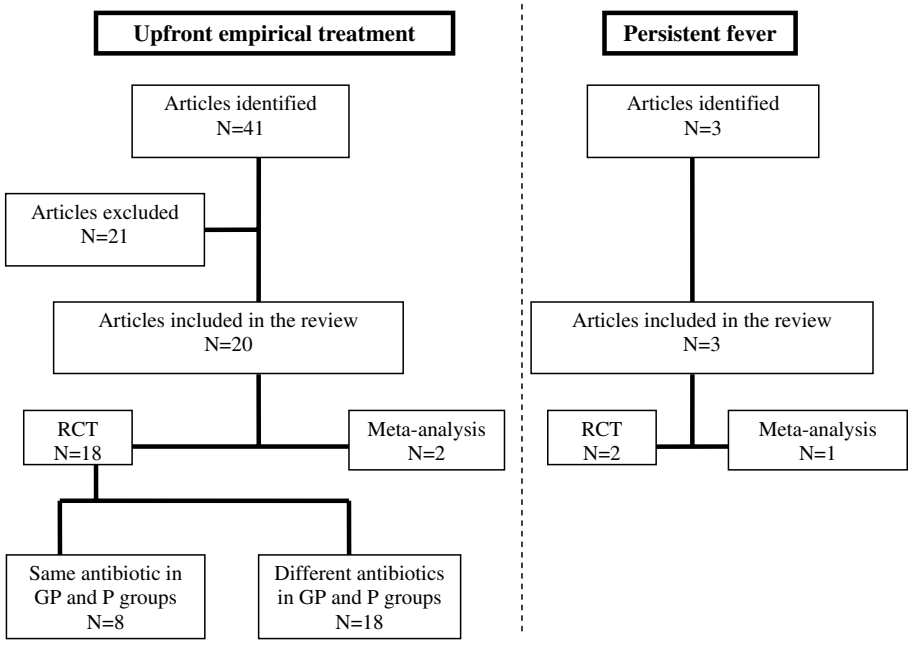
The questionnaire on clinical practices for the management of infections in neutropaenic patients with acute leukaemia comprised a section on the use of anti-Gram-positive antibiotics. The following information was collected: upfront empirical use of anti-Gram-positive antibiotics, addition of anti-Gram-positive antibiotics in persistently febrile neutropaenic patients and special conditions requiring the upfront addition of anti-Gram-positive antibiotics.

3. Results

3.1. Question 1: Is the use of anti-Gram-positive antibiotics (i.e. glycopeptides, oxazolidinones or streptogramins) indicated for upfront empirical therapy of febrile neutropenia in patients with acute leukaemia?

3.1.1. Glycopeptides

Using a search strategy including Medline, international meetings, 2 meta-analyses, 3 national guidelines and 39 clinical trials assessing the role of upfront use of glycopeptides in febrile neutropaenic patients have been identified (Fig. 1). Of the 39 clinical trials, 21 have been excluded for the following reasons: comparison of two different glycopeptides without a placebo group ($n = 7$), therapy with various broad-spectrum antibiotic regimens with the same glycopeptide in the treatment groups ($n = 6$), non-comparative studies ($n = 3$), dupli-



RCT: randomised clinical trial

GP: glycopeptide

P: placebo

Fig. 1 – Empirical use of anti-Gram-positive antibiotics in neutropaenic patients either as upfront treatment or in case of persistent fever: identification and selection of articles.

cate publication ($n = 2$), administration of two different beta-lactams in the group not receiving a glycopeptide ($n = 1$), use of historical controls ($n = 1$) and comparison of vancomycin to flucloxacillin without a placebo group ($n = 1$).

Therefore, 18 randomised controlled trials that have assessed the role of glycopeptides as upfront empirical therapy for febrile neutropaenic adult patients were reviewed (Table 1). All the studies had been published between 1986 and 1993 and examined the efficacy and toxicity of antibiotic regimens incorporating a glycopeptide antibiotic (vancomycin or teicoplanin) or not. Only 2 of 18 studies were double-blinded.[6,7] Three of 18 were multicentre studies.[8–10] The largest study that was conducted in 35 centres enrolled 747 patients, whereas the smallest study enrolled 46 patients.[8,11] In eight trials, both groups of patients were treated with the same broad spectrum antibiotic regimen, consisting either of ceftazidime monotherapy or of an anti-pseudomonal beta-lactam combined with an aminoglycoside.[6,8,9,11–15] In 10 studies, different broad-spectrum antibiotic regimens were used for patients who did or did not receive a glycopeptide.[7,10,16–23]

Two meta-analyses have been published on the role of glycopeptides in the initial empirical therapy of febrile neutropaenic cancer patients. Vardakas et al. performed a meta-analysis of 14 (i.e. Refs. 6–10,13–19,21,22) of the 18 randomized trials that included a total of 2413 patients.[24] A subgroup analysis was also performed on six studies in which the same broad-spectrum antibiotic regimen was used in both treatment arms (i.e. Ref. 6,8,9,13–15). The second meta-analysis was published by Paul et al. and included 13 studies (including Refs. 6,8–10,13,15,32,33) and 2392 patients.[25] Studies of flucloxacillin, sulphamethoxazole and cephalothin were also included in this meta-analysis as were two clinical trials (Refs. 32,33) in which glycopeptides were added for persistent fever. These meta-analyses extracted data on efficacy (including all-cause mortality, success without or with modification of empirical antibacterial therapy, duration of fever, breakthrough infections) and adverse events. After assessment of heterogeneity, pooled odds ratios or relative risk ratios were calculated by Maentel-Haenszel fixed effects (in absence of heterogenicity) or DerSimonian-Lard random effects models (in presence of heterogenicity), respectively.

Assessment of efficacy. As shown in Table 2, *all-cause mortality* which was reported in 11 of the 18 trials ranged between 0% and 18%. In one study performed in children, one death was reported in 101 patients.[7] In four studies, the mortality was higher than 10% (11–18%).[10,12,15,16] In 10 studies no significant difference in mortality between patients treated with or without a glycopeptide was observed. In only one study, in which a low dose of ceftazidime (1g q8h) had been used, was the mortality of glycopeptide-treated patients lower than that of control patients.[10] The largest study, performed by the EORTC, showed that the mortality in patients with Gram-positive bacteraemia was low (3 of 135 episodes) and that none of these deaths occurred within the first 3 days of therapy.[8] Thus, these results suggested that clinicians could wait for microbiological documentation of Gram-positive infection before adding a glycopeptide antibiotic. No study

Table 1 – Clinical trials assessing the role of glycopeptide antibiotics as part of the empirical therapy of fever in neutropaenic cancer patients

First author and year	N	Type of study	Number of centres	Glycopeptide	Study endpoints
Karp, 1986	60	RCT-DB	Single	Vancomycin	Further Gram-positive infections, time to defervescence
Del Favero, 1987	47	RCT	Single	Teicoplanin	RR
Granowetter, 1988	101[a]	RCT	Single	Vancomycin	RR–RR′
Shenep, 1988	101	RCT-DB	Single	Vancomycin	RR, breakthrough bacteraemia, death
Micozzi, 1990	46	RCT	Single	Teicoplanin	RR–RR′, death
Spencer, 1990	59	RCT	Single	Teicoplanin	RR
Meunier, 1990	75	RCT	Single	Teicoplanin	RR, death
De Pauw, 1990	103	RCT	Single	Teicoplanin	RR–RR′
EORTC, 1991	747	RCT	35	Vancomycin	RR, RR in G+, time to defervescence, death
Novakova, 1991	103	RCT	Single	Teicoplanin	RR–RR′, time to defervescence, death
Viscoli, 1991	193	RCT	Single	Vancomycin	RR, death
Riikonen, 1991	89	RCT	Single	Vancomycin	RR, time to defervescence
Bosseray, 1992	87	RCT	Single	Vancomycin	RR
Martino, 1992	158	RCT	Single	Teicoplanin	RR, breakthrough bacteraemia, death
Kelsey, 1992	71	RCT	Single	Teicoplanin	RR, death
Ramphal, 1992	127	RCT	2	Vancomycin	RR–RR′, death, superinfections
Micozzi, 1993	104	RCT	Single	Teicoplanin	RR, time to defervescence, death
Pico, 1993	102	RCT	2	Vancomycin	Life-threatening infection

RCT, randomised controlled trial; DB, double-blinded; RR, response rate without modification of empirical antibiotic regimen; RR′, response rate with modification of empirical antibiotic regimen.
a Groups treated with ceftazidime or ceftazidime plus vancomycin included and group treated with cephalotin plus carbenicillin plus gentamicin excluded from the analysis.

Table 2 – Mortality and response rate without modification of therapy in clinical trials assessing the role of glycopeptide antibiotics as part of the empirical therapy of fever in neutropaenic cancer patients

First author and year	Mortality		Response rates without modification	
	Without glycopeptide	With glycopeptide	Without glycopeptide	With glycopeptide
Del Favero, 1987	NA	NA	56%	82%
Granowetter, 1988	NA	NA	75%	70%
Shenep, 1988	1/48 (2%)	0/53 (0%)	62%*	85%*
Micozzi, 1990	NA	NA	32%*	80%*
Spencer, 1990	NA	NA	47%	66%
Meunier, 1990	9/50 (18%)	8/50 (16%)	67%	67%
De Pauw, 1990	6/51 (12%)	4/52 (8%)	49%	63%
Viscoli, 1991	7/95 (7%)	2/98 (2%)	66%	77%
EORTC, 1991	19/370 (5%)	24/377 (6%)	63%*	76%*
Novakova, 1991	9/60 (15%)	7/60 (12%)	49%	63%
Riikonen, 1991	NA	NA	81%*	59%*
Ramphal, 1992	6/63 (10%)	7/64 (11%)	56%	61%
Bosseray, 1992	NA	NA	80%	80%
Martino, 1992	4/83 (5%)	5/75 (7%)	51%	60%
Kelsey, 1992	2/29 (7%)	1/29 (3%)	49%*	78%*
Micozzi, 1993	3/56 (5%)	3/58 (5%)	41%*	60%*
Pico, 1993	10/69* (14%)	0/33* (0%)	NA	NA

* Statistically significant difference.

was designed with enough power to show a significant difference in all-cause mortality. However, the meta-analysis by Vardakas et al. provided some useful information on this issue.[24] Up-front addition of a glycopeptide antibiotic did not reduce all-cause mortality either in overall study population (odds ratio 0.67, 95% CI 0.42–1.05) or in the subgroup analysis, including six trials in which 405 patients received the same broad-spectrum antibiotic regimens in both treatment arms (odds ratio 1.05, 95% CI 0.52–2.00). The meta-analysis by Paul et al. confirmed these findings (relative risk 0.96, 95% CI 0.58–1.26).[25]

Success without modification of the initial antibiotic regimen was the second endpoint assessed in 16 of 18 trials (Table 2). Up-front use of a glycopeptide was associated with significantly higher success rates in five studies.[7,8,11,21,22] In addition, a trend in favour of the glycopeptide group was observed in seven other studies. The only trial performed in 89 febrile episodes in children reported response rates of

82% in patients treated with imipenem alone and 59% in those treated with a combination of ceftazidime and vancomycin.[18] In the meta-analysis by Vardakas et al. that comprised data from 11 trials and 1812 episodes of fever, the addition of a glycopeptide antibiotic to the empirical antibiotic regimen was associated with a higher success rate compared to that of regimens not including a glycopeptide (odds ratio 1.63, 95%CI 1.17–2.28).[24] The same difference was observed in sub-analyses of patients with microbiologically documented infections (odds ratio 2.03, 95% CI 1.39–2.97), in patients with bacteraemia (odds ratio 1.80, 95% CI 1.23–2.63) and in patients with neutropenia of less than 100 cells/μl (odds ratio 2.24, 1.15–4.39). However, the success rate without modification should be interpreted with great caution, especially in trials that were not double-blinded as there was an obvious bias towards an addition of a glycopeptide antibiotic in persistently febrile patient when it was not part of the initial antibiotic regimen.[8,15] Indeed, additional analyses did not show differences in terms of the *duration of fever* in patients treated with or without glycopeptides or in the proportion of patients with persistent fever at each day after initiation of empirical therapy suggesting that the modification of treatment might have been influenced by factors other than true microbiological or clinical failures.[8,9,15,22] The meta-analysis by Vardakas et al. also confirmed the observation that use of a glycopeptide did not reduce the time to defervescence.[24]

Success rates with modification of the empirical antibiotic regimen, which was assessed in five studies, were similar in patients who did or did not receive glycopeptides.[11,12,14,15,23] However, if modification of the allocated treatment is not evaluated as a failure, causes of failures are then limited to death and breakthrough bacteraemia and success rates are in the range of 90%. Therefore, the likelihood of showing a difference, if it exists, is very limited especially in studies with relatively small sample sizes (i.e. 100–150 patients).

Breakthrough infections occurred in 13–15% of febrile neutropaenic episodes (7 studies). The risk of breakthrough infections was unchanged in patients who had received a glycopeptide.[8,9,15,17,19,21,22] Data from the meta-analysis by Vardakas et al. based on four trials and 1188 episodes of febrile neutropenia confirmed that the addition of a glycopeptide did not exert any impact on the development of breakthrough infections (odds ratio 1.18, 95%CI 0.71–1.98).[24] In contrast, the meta-analysis by Paul et al. reported a reduction of bacterial breakthrough infections (relative risk 0.38, 95%CI 0.24–0.59) and of Gram-positive breakthrough infections (relative risk 0.21, 95%CI 0.11–0.37).[25] The occurrence of breakthrough bacteraemia was reported in four studies. Unfortunately, the low number of events (0–2 cases per group) that occurred in three of these four studies was insufficient to draw any conclusion.[18,21,23] One study performed in children in a single centre showed that the number of breakthrough bacteraemias due to Gram-positive bacteria was significantly higher in the group who did not receive a glycopeptide (9 of 48 patients) than in the group who did (1 of 53 patients).[7] Obviously, epidemiological data which may differ between cancer centres are essential when choosing an initial antibiotic regimen. None of these studies performed between 1985 and 1993 reported the emergence of vancomycin-resistant enterococci (VRE). However, by the end of the 1990s, VRE had become a significant concern in cancer patients, especially in US centres. Vancomycin use was shown to be a risk factor for VRE bloodstream infections.[26] An infection control policy reducing vancomycin use was associated with a decrease of the total incidence of VRE infections including VRE bloodstream infections.[27] Although VRE are less of a problem in Europe than in the US, there have been reports of VRE infections in European cancer centres, which strengthens the argument in favour of restricted use of glycopeptide antibiotics.

Assessment of adverse events. Most of the trials showed a trend towards an increased frequency of adverse events in patients treated with glycopeptides. This trend was confirmed in the meta-analyses by Vardakas et al. (odds ratio 4.98, 95% CI 2.91–8.55) and Paul et al. (relative risk 2.33, 95% CI 1.43–3.80).[24,25] In three studies there was a significantly higher incidence of skin rash in glycopeptide-treated patients.[8,9,17] Nephrotoxicity also occurred more often in glycopeptide-recipients, especially in patients who were treated simultaneously with an aminoglycoside (6% in the vancomycin group versus 2% in group not treated with vancomycin) or with amphotericin B.[8,9] However, no study reported the need of haemodialysis following the administration of glycopeptides. The meta-analyses confirmed that nephrotoxicity occurred more frequently in patients treated with a glycopeptide (Vardakas: odds ratio 2.10, 95% CI 1.12–3.95; Paul: relative risk 1.43, 95% CI 1.06–1.94).[24,25]

3.1.2. *Oxazolidinones and streptogramins*

A recent double-blind, multicentre study compared the safety and efficacy of linezolid to that of vancomycin in febrile, neutropaenic patients with cancer and proven or suspected Gram-positive infections.[28] The study, which enrolled patients at the onset of fever and patients with persistent fever, showed similar success rates in patients treated with linezolid and vancomycin (87.3% versus 85.2%, difference: 2.1%, 95% CI, −4.1 to 8.1). The safety of linezolid was comparable to that of vancomycin (serious adverse events in 12% and 16% of cases; treatment discontinuations related to adverse events occurred in 4% and 5% of cases; no difference in hematological adverse events or bone marrow recovery). Yet, given the absence of a placebo group, this study does not allow conclusions to be drawn on the questions addressed in these guidelines. No data have been reported on the use of streptogramins in neutropaenic cancer patients.

3.2. *Question 2: Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated in persistently febrile neutropaenic patients with acute leukaemia?*

Persistence of fever despite administration of broad-spectrum antibiotics is a common problem in neutropaenic patients. Antibiotic therapy is frequently modified in patients in whom fever persists after 72–96 h of empirical therapy despite the absence of clinical deterioration and documentation of an infection caused by a microorganism resistant to the allocated antibiotic regimen. With the increased frequency of

Gram-positive infections observed since the mid 1980s, adding glycopeptide antibiotics to the empirical regimen has been popular modification of therapy among physicians in charge of neutropaenic cancer patients.[29–31]

Two double-blinded studies with a similar design have examined whether there is an indication for adding a glycopeptide in neutropaenic cancer patients who remained febrile 48–96 h after initiation of broad-spectrum antibiotic therapy (Table 3). Both studies excluded patients with documented Gram-positive bacteria resistant to beta-lactam antibiotics and patients with catheter-related infections. In a large multicentre study conducted by the EORTC in 763 eligible patients treated empirically with piperacillin-tazobactam, 165 patients who remained febrile 48–60 h after initiation of therapy were randomized to receive either vancomycin (86 patients) or placebo (79 patients).[32] The time to defervescence, defined as a period of three consecutive days with a temperature below 38 °C, was similar in the 2 treatment groups. The number of patients who became afebrile under protocol therapy was 49% in the vancomycin group and 46% in placebo group. In addition, there was no difference in terms of mortality (5% in vancomycin group and 10% in placebo group), occurrence of breakthrough Gram-positive infections or proportion of patients for whom amphotericin B was added empirically. In the second study, conducted in a single centre, 114 patients who remained febrile 72–96 h after initiation of imipenem-cilastatin were randomized to receive either teicoplanin or placebo.[33] The number of patients who had defervesced 3 days after randomisation was 45% in the teicoplanin group and 47% in the placebo group. Mortality rates were also similar in both treatment groups (11% in the teicoplanin group and 7% in the placebo group). Taken together, the results of these two studies clearly indicate that the addition of a glycopeptide antibiotic did not have any impact on morbidity or mortality. This was confirmed by the meta-analysis of Paul et al. (relative risk of treatment failure 0.61, 95%CI 0.18–2.09).[25]

3.3. *Question 3: Are there specific indications justifying the upfront use of anti-Gram-positive antibiotics as part of the empirical therapy?*

There are no data on specific indications (e.g. increased risk for resistant Gram-positive infections, severe sepsis/septic shock, suspected skin/soft tissue or catheter infections) for the upfront use of anti-Gram-positive antibiotics when combined with broad-spectrum antibiotics in febrile neutropaenic cancer patients.

3.3.1. *Questionnaire on clinical practice in Europe*

Of 37 experts, only one considered that anti-Gram-positive antibiotics should be given as up-front empirical therapy of fever in neutropaenic cancer patients. However, when there was suspicion of catheter-related infections and skin and soft tissue infections, use of an anti-Gram-positive antibiotics was favoured by 26 and 24 of the 34 consulted experts, respectively. Eighteen of the 34 experts also elected to use anti-Gram-positive antibiotics in patients with hypotension or shock. Finally, 11 of 34 experts favoured the use of an anti-Gram-positive antibiotic in patients with persistent fever.

4. Recommendations (Table 4)

4.1. *Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated for upfront empirical therapy of febrile neutropenia in acute leukemic patients?*

Answer: No, Grading I D.

Comments. The review of 18 studies performed between 1986 and 1993 as well as two recently published meta-analyses do not support the use of glycopeptides at the onset of fever in neutropaenic cancer patients. Although the up-front addition of a glycopeptide antibiotic was associated with better response rates without modification of the empirical antibiotic regimen, glycopeptides had no effects on several clinically relevant endpoints such as time to defervescence, occurrence of breakthrough infections and mortality. By contrast, the use of glycopeptides was associated with increased adverse events, mainly nephrotoxicity and skin rashes. Broad use of glycopeptides has been shown to be a risk factor for the development of bacteraemia due to vancomycin-resistant enterococci. Therefore, the absence of significant benefit and the risk of emergence of resistance to glycopeptides are important arguments favouring the restricted use of glycopeptides in these patients. No clinical data are available on oxazolidinones or streptogramins.

4.2. *Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated in persistently febrile neutropaenic patients with acute leukaemia?*

Answer: No, Grading I D.

Comments. The addition of a glycopeptide to broad-spectrum antibiotic is not recommended in neutropaenic patients with persistent fever as it has no impact on all-cause mortal-

Table 3 – Defervescence and all-cause mortality in clinical trials assessing the efficacy of glycopeptides in persistently febrile neutropaenic cancer patients

First author and year	Design	Regimens	Defervescence	All-cause mortality
Erjavec, 2000	Single centre, double-blinded	Teicoplanin, $n = 56$ versus Placebo, $n = 58$	44.6% versus 46.6%	10.7% versus 6.9%
Cometta, 2003	Multicentre, double-blinded	Vancomycin, $n = 86$ versus Placebo $n = 79$	49% versus 46%	5% versus 10%

Table 4 – CDC grading of evidence and level of recommendation for the use of glycopeptide antibiotic in neutropaenic cancer patients

Circumstances	Addition of glycopeptide	Quality of evidence and level of recommendation
Fever onset	Not recommended	I D
Persistent fever	Not recommended	I D
Predominance in the local epidemiology of resistant Gram-positive (e.g. methicillin-resistant *S. aureus*, penicillin-resistant *S. pneumoniae*)	Recommended	III C
Severe sepsis and septic shock	Recommended	III C
Skin and soft tissue infections (including catheter-related infections)	Recommended	III C

ity, on resolution of fever, on the time to defervescence or on the occurrence of breakthrough Gram-positive infections. No clinical data on oxazolidinones or streptogramins are available.

4.3. *Are there specific situations in which up-front empirical therapy with anti-Gram-positive antibiotics might be justified?*

Answer: Yes, Grading III C.

Specific situations. In centres where *resistant Gram-positive bacteria* (i.e. methicillin-resistant *S. aureus* or penicillin-resistant streptococci) are *predominant*, it is reasonable to include a glycopeptide in the empirical antibiotic regimen. The same reasoning also applies to patients known to be colonized with resistant microorganisms. However, *S. aureus* bacteraemias are rare in neutropaenic cancer patients, accounting only for 1–2% of febrile episodes in large clinical trials.[29,34,35] In case of colonisation with penicillin-resistant pneumococci, the doses of carbapenems, cefepime or piperacillin/tazobactam recommended for the treatment of neutropaenic patients should provide serum levels above the MIC of these microorganisms for prolonged periods of time (Recommendation: III C). If used for upfront therapy, glycopeptides should be stopped as soon as an infection due to resistant bacteria is ruled out, i.e. 48–72 h after initiation of therapy in most instances. Data from a single study suggest that linezolid may be an alternative to glycopeptides. No data on streptogramins are available.

Severe sepsis and septic shock occur in 1–2% of febrile neutropaenic episodes.[34,36] However, the incidence of these complications might be underestimated, as septic shock often is an exclusion criterion in many clinical studies. Although no data are available, it is recommended to use a glycopeptide antibiotic in patients in whom febrile neutropenia is accompanied by severe sepsis or septic shock. Indeed, in a logistic regression analysis of patient's outcome performed in 909 neutropaenic cancer patients with bacteraemia, the risk of fatal outcome was significantly increased in patients with hypotension (Recommendation III C).[37] Shock and respiratory distress syndrome have also been described in patients with viridans streptococcal bacteraemia.[38] Bacteraemias due to viridans streptococci accounted for 3–5% of all febrile episodes. Data showing a decreased susceptibility of viridans streptococci to penicillin have led some authors to recommend the administration of glycopeptides to febrile neutropaenic patients at increased risk of infections caused by these microorganisms.[39] The clinical complications of shock or respiratory distress syndrome have been typically observed in patients with severe mucositis who have received fluroquinolone prophylaxis and have been treated with ceftazidime monotherapy for empirical therapy of febrile neutropenia.[40] However, shock or respiratory distress syndrome associated with viridans streptococcal infections have occurred much less frequently in recent clinical trials using cefepime, piperacillin-tazobactam or carbapenems as these antibiotics exhibit better activity than ceftazidime against viridans streptococci.[34,35,41–44] These observations therefore suggest that the use of a glycopeptide is not justified for prevention of complications associated with infections due to viridans streptococci.

Clinical evidence of *skin and soft tissue infections, including catheter tunnel infections*, would also justify the empirical addition of a glycopeptide antibiotic since the majority of these infections are due to methicillin-resistant coagulase-negative staphylococci. However, no data support this recommendation (Recommendation III C).

5. Conclusions

Despite the frequency of Gram-positive infections in neutropaenic cancer patients, neither the individual studies nor the two meta-analyses performed on these studies support the empirical use of glycopeptide antibiotics either at fever onset or in the case of persistent fever despite empirical broad-spectrum antibiotic therapy. However, clinical conditions that may justify the up-front use of a glycopeptide include the predominance in the local epidemiology of resistant Gram-positive bacteria, severe sepsis or septic shock, or a high suspicion of skin and soft tissue infections, including catheter tunnel infections. A survey among experts suggested that practices in Europe are in line with these recommendations. In recent years, several new antibiotics with Gram-positive coverage have been licensed, such as oxazolidinones or streptogramins. However, little or no information, respectively, is available on the efficacy and safety of these agents in neutropaenic cancer patients.

Conflict of interest statement

A. Cometta has received grants and research supports from Bayer and Wyeth.

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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*

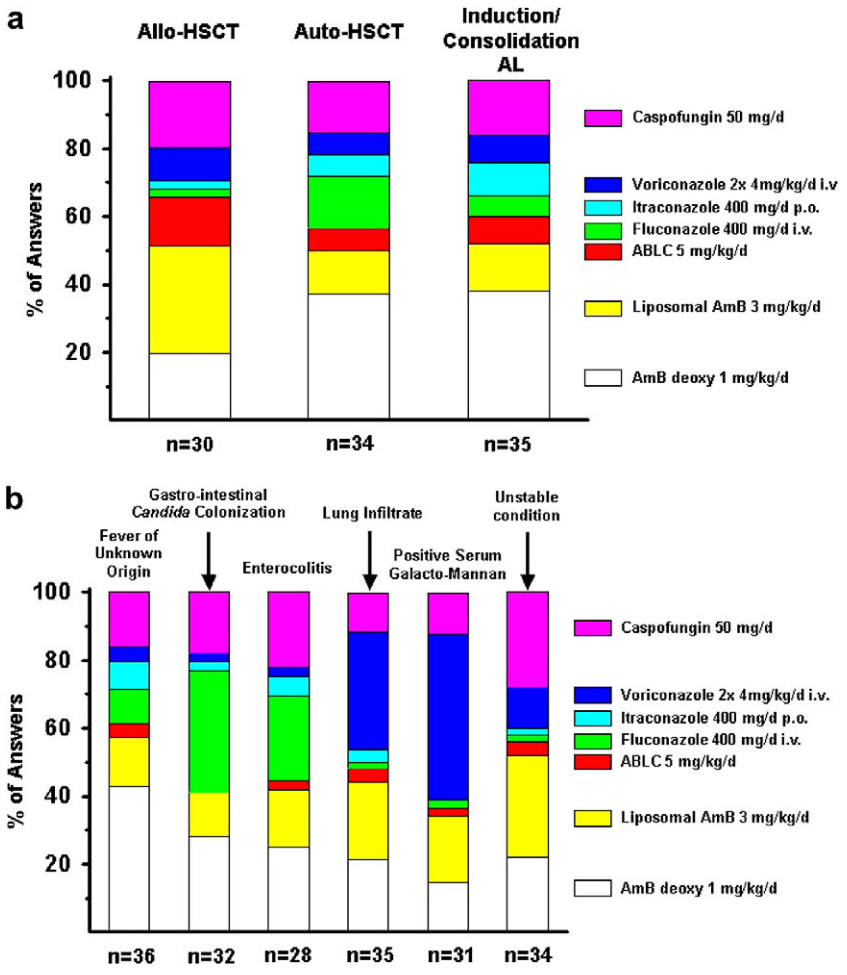

Fig. 1 – Choices of empirical antifungal agents in persistently febrile neutropaenic patients: (a) choice according to the underlying condition; (b) choice according to clinical presentation/condition.

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:

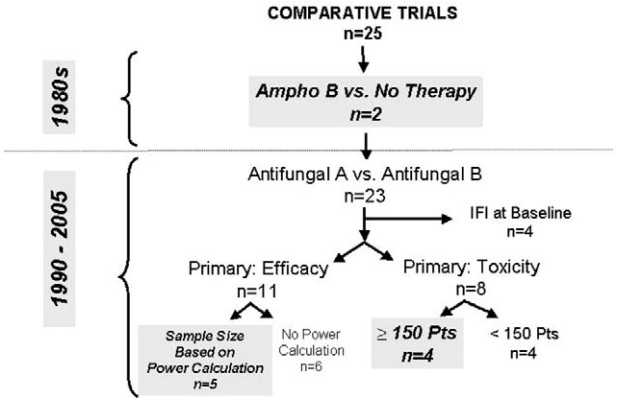

Fig. 2 – Selection of comparative clinical trials on empirical antifungal therapy in persistently febrile neutropaenic cancer patients.

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

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Primary antifungal prophylaxis in leukaemia patients ☆

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ABSTRACT

These recommendations have been developed by an expert panel following an evidence-based search of the literature assessing the role of primary antifungal prophylaxis in patients with acute leukaemia or stem cell transplantation. 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

Patients with acute leukaemia (AL) or myelodysplastic syndrome (MDS) who undergo successive cycles of myelosuppressive chemotherapy or who undergo haematopoietic stem cell transplantation (HSCT) have a high incidence of proven and probable mould and yeast infections. Treatment of these infections is often ineffective due to delays in diagnosis, resulting in high mortality rates.[1–3] Besides, signs and symptoms of infection are usually non-specific and these infections are commonly missed by culture or because of the inability to perform biopsies.[4] Consequently, primary antifungal chemoprophylaxis (PAC) has been recommended and has become routine practice in many European Leukaemia and HSCT centres.[5] However, in spite of the burden of published data on PAC, drawing solid scientific conclusions remains challenging.[6] This highlights the need for evidence-based European recommendations.

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2. Methods

The European Conference on Infections in Leukaemia (ECIL) recommendations on PAC are based on a review of the English-language literature following a predefined methodology (see introductory chapter) and using the following key words: neutropenia, stem cell transplantation, azole, prophylaxis, antifungal, prevention, fungal infection and aspergillosis.

Many of the published studies were observational or used historical controls. Such approaches, even when properly matched, are inevitably biased. We therefore decided that preferably prospective, randomised trials would be considered for efficacy assessment (quality of evidence, level I). Drawing firm conclusions remained challenging, however, given the non-blinded nature of many of these studies and the risk of statistical type II errors due to an insufficient sample size.

The risk of acquiring an invasive fungal infection (IFI) varies with the case mix of the study population. Allogeneic HSCT recipients with graft-versus-host disease or relapsed leukaemia patients are at higher risk than most other haematology patients; however, these high-risk, critically-ill subgroups were frequently under-represented or even excluded from prophylactic trials. Diluting the study population with patients at low risk (autologous transplants, short duration of neutropenia) favours demonstration of equivalence of two regimens. As a consequence, sample size, case mix and treatment imbalances impacted heavily on the strength of our recommendations (A–E).

A reduction of the number of proven and probable IFIs and an improvement in fungal-free survival and overall survival are the main objectives of PAC. Therefore, these end-points were given the highest priority. These end-points were however not always reported. Hence, surrogate end-points for efficacy were reported, including the impact on persistent fever, the frequency of possible IFIs, the use of empirical antifungal therapy and the mortality attributable to IFI. Although these latter end-points are poorly defined and usually highly subjective, mainly due to divergence in clinical management, we still tried to rate and to incorporate the impact of PAC on these different components before generating an overall recommendation. Toxicity and tolerability data, drug interaction profiles, patient's compliance and quality of life assessments, if available, were also included in the assessment of the strength of the recommendation (A–E).

According to the common methodology used in all working groups in preparation of the ECIL meeting, a list of priority questions were proposed by the organizing committee and redefined by the working group, including:

- Can we identify patient populations that are likely to benefit from PAC?
- Is PAC having an impact on the incidence of invasive fungal infections (yeast versus mould), on overall mortality, on fungal infection-related mortality, on the use of empirical antifungal therapy and on toxicity?
- Is PAC associated with increased resistance or selection of specific pathogens?
- How long should PAC be continued?
- Should serum levels of specific antifungal compounds be measured and what is the target level?

3. Results

3.1. *Questionnaire*

Eighty-seven percent of the 38 investigators answering the questionnaire gave antifungal prophylaxis: 85% gave prophylaxis to allogeneic HSCT, 63% to autologous HSCT and to AL patients. The distribution of antifungal agents is shown in Table 1. For allogeneic HSCT, the duration of prophylaxis was highly variable and ranged from including the neutropenic phase only (18%) to until day +100 (16%) or resolution of graft-versus-host disease (13%) or both (16%). The main reason for giving prophylaxis was to prevent superficial fungal infections (21%), yeast (25%) or mould (11%) infections specifically, invasive fungal infections in general (13%) and to reduce mortality (13%). Only 15 of the 38 investigators considered their attitude supported by the literature (see Table 2).

3.2. *Literature analysis*

Patients diagnosed with leukaemia represent a heterogenous population in terms of evolution of their underlying disease (acute versus chronic), intensity of therapy (intensive chemotherapy ± allogeneic transplantation versus a wait-and-see policy) and risk of developing opportunistic infections. Although future treatment options may render the so-called low-risk leukaemia patients (chronic leukaemia and low-risk MDS patients) more at risk for invasive fungal infections, the population that is nowadays most likely to benefit from antifungal prophylaxis consists of patients with an expected incidence of invasive fungal infections of at least 10%. This population includes acute leukaemia and high-risk MDS patients as well as patients undergoing haematopoietic stem cell transplantation (allogeneic > autologous). As such, our recommendations will only apply to these latter groups.

Table 1 – Results of the questionnaire (*N* = 38): distribution of antifungal agents used in prophylactic regimens according to the underlying condition

Agent (%)	Allogeneic HSCT	Autologous HSCT	Induction chemotherapy
Fluconazole	**57.1**	**57.1**	**55**
Itraconazole capsules	7.1	9.5	5
Itraconazole oral solution	**21.4**	**14.3**	**20**
Itraconazole intravenous	3.6	4.8	5
Voriconazole	3.6	4.8	5
Liposomal Ampho B	3.6	–	–
Nystatin	10.7	14.3	15
Non-absorbable Ampho B	**17.9**	**19.0**	**25**
Aerosolized Ampho B	7.1	–	–

Table 2 – Antifungal prophylaxis in leukaemia patients: ECIL recommendations

Allogeneic haematopoietic stem cell transplantation	
Fluconazole 400 mg qd intavenous (i.v.)/oral	AI
Itraconazole 200 mg IV followed by oral solution 200 mg bid	BI[b]
Posaconazole 200 mg tid oral	AI[c]
Micafungin 50 mg qd i.v.	CI
Polyene[a] i.v.	CI
Induction chemotherapy acute leukemia	
Fluconazole 50–400 mg qd i.v./oral	CI
Itraconazole oral solution 2.5 mg/kg bid	CI[b]
Posaconazole 200 mg tid oral	AI[c]
Candins i.v.	No data
Polyene[a] i.v.	CI–CII

a Includes low-doses of amphotericin B deoxycholate and lipid formulations of amphotericin B The ECIL recommendation for aerosolised amphotericin B deoxycholate is DI.
b May be limited by drug interactions and/or patient tolerability.
c Provisional recommendation (see text).

3.2.1. Azoles

– *Fluconazole:* Fluconazole is an attractive agent for antifungal prophylaxis because of its systemic effect, ease of administration and favourable safety profile. In the 1990s, the papers by Goodman and Slavin have set the trend for the widespread use of fluconazole prophylaxis.[7,8] Although a significant reduction of the incidence of IFI and of the overall mortality has only been shown for patients undergoing HSCT, fluconazole prophylaxis has also become the standard of care in patients undergoing intensive chemotherapy for AL and MDS.[9–12] In a meta-analysis by Bow et al., fluconazole prophylaxis reduced the use of parenteral antifungal therapy (including the empirical use), the incidence of superficial fungal infections and of invasive *Candida* infections, and the fungal infection-related mortality.[13] In addition, fluconazole prophylaxis decreased the overall mortality, but only in the subset of patients with prolonged neutropenia and in those undergoing HSCT.[13,14] A daily dose of 400 mg is recommended. Subsequent studies have suggested but not proven that lower daily doses of fluconazole (50–200 mg) may suffice for fungal prevention during induction chemotherapy.[12] Of note, fluconazole is ineffective against moulds and *Candida krusei* and displays a dose-dependent activity against some strains of *C. glabrata*. This spectral shortcoming results in the occurrence of breakthrough infections.
ECIL recommendation:
  - allogeneic HSCT: fluconazole 400 mg/day: AI;
  - autologous HSCT or acute leukaemia: fluconazole 50–400 mg/day: CI.
– *Itraconazole:*
  - *Capsules*: Itraconazole displays a broad spectrum of activity, including *Aspergillus* species. In randomised trials using the capsule formulation (200–400 mg/day), the incidence of IFIs was not significantly different from the respective comparator drugs (fluconazole 100 mg/d; placebo ± oral amphotericin B).[15–17]
  - *Oral solution*: The increased bioavailability of the oral solution formulation has been demonstrated in autologous HSCT recipients and in patients with AL. Data on the prophylactic efficacy of this formulation in haematology patients are available from five prospective, randomised multicentre trials.[18–22] However, no single study has convincingly demonstrated a reduction in the number of *Aspergillus* infections or an improvement in the overall or fungal-free survival. Lack of superiority may result from flaws in trial methodology and patient recruitment, including the use of a non-blinded design,[19] the exclusion of allogeneic HSCT recipients and the absence of regimens that are more frequently associated with IFIs (e.g. high-dose cytarabine, with or without fludarabine).[18] According to a recent meta-analysis however, itraconazole oral solution (at least 400 mg/day) effectively prevents proven invasive fungal infections (including invasive aspergillosis) and reduces mortality from these infections.[23]
  - *Intravenous followed by oral solution*: The prolonged use of adequately dosed itraconazole (200 mg intravenous (i.v.) followed by the oral solution 200 mg bid) versus fluconazole (400 mg oral or i.v.) has been evaluated in two open-label studies in myeloablative allogeneic HSCT recipients.[24,25] Both the studies have demonstrated a higher efficacy of itraconazole in preventing invasive mould infections. However, the study of Winston et al. was hampered by imbalances in patients characteristics in favour of itraconazole,[24] whereas that of Marr et al. (using a high-dose of 2.5 mg/kg tid) showed a 36% dropout rate in the itraconazole arm due to intolerance and toxicity.[25] This latter observation is consistent with the findings of a recent meta-analysis.[26] In addition, Marr reported unexpected liver toxicity when itraconazole was used concomitantly with cyclophosphamide.[27] So, the potential for hazardous drug interactions represents another drawback.
  ECIL recommendation:
    - in allogeneic HSCT: itraconazole 200 mg/day IV followed by oral solution: BI;
    - in autologous HSCT and acute leukaemia: *itraconazole oral solution 2.5 mg/kg bid: CI;*
    - itraconazole capsules: EI.
  - *Should itraconazole levels be measured?* Given the marked variations in bioavailability and the significant dose–response relationship, therapeutic drug monitoring is recommended to ensure adequate plasma levels (a thorough concentration of at least 500 ng ml^{-1} itraconazole measured by high-performance liquid chromatography) at steady state (*ECIL recommendation BII*).[28]

3.2.2. Aerosolized amphotericin B (AMB) deoxycholate

Contrary to yeast infections, mould infections are primarily airborne. Thus, delivering high concentrations of AMB to the airways by aerosolising the drug represents an appealing approach. Unfortunately, the only randomised study in this field found no difference in the incidence of invasive pulmonary aspergillosis or in overall mortality between patients who

received inhalations and those who did not. Moreover, intolerance led to the premature discontinuation in ~30% of cases.[29] It remains to be seen whether the use of a lipid formulation of AmB or a powder formulation will increase efficacy and tolerance.

ECIL recommendation: DI.

3.2.3. *Systemic low-dose AMB deoxycholate*

Some investigators have examined the use of low-doses of intravenous AMB (ranging from 0.5 mg/kg/day to <0.1 mg/kg/day), with or without intranasal sprays. In retrospective analysis, this approach decreased both the incidence of invasive aspergillosis and the transplant-related mortality in allogeneic HSCT recipients. However, these results are inconclusive due to the use of historical controls and due to the presence of confounding environmental and prognostic factors.[30,31]

ECIL recommendation: CII.

3.2.4. *Lipid formulations of AMB*

Two placebo-controlled, double-blind randomised studies (using liposomal AMB 1 mg/kg/day or 2 mg/kg three times weekly) have been performed in HSCT recipients and in patients receiving chemotherapy.[32,33] However, these studies were not sufficiently powered to detect a superiority of liposomal AMB over placebo. Thus, although associated with an encouraging trend towards a reduced incidence of IFI, the difference could not reach statistical significance. Unexpectedly, no single case of proven invasive aspergillosis was observed in these series, not even in the control group. A randomised trial comparing fluconazole versus ABCD was terminated prematurely because of severe infusion-related side effects in the ABCD-arm.[34]

ECIL recommendation: CI.

3.2.5. *Echinocandins*

The echinocandins display activity against *Candida* and *Aspergillus* species. These agents induce little toxicity and are not metabolised through the cytochrome P450 enzymes. Therefore, echinocandins represent a safe alternative to fluconazole and yield activity against invasive aspergillosis. The prophylactic efficacy of micafungin (50 mg) was compared with fluconazole (400 mg) in a double-blind, multicenter study during the neutropenic phase of HSCT.[35] The study concluded that the overall efficacy of micafungin was superior to that of fluconazole (including decreased use of empirical antifungal therapy but no difference in overall mortality). Unfortunately, this study included a large number (70%) of autologous and low-risk allogeneic transplants and did not address the prevention of late IFIs.

ECIL recommendation:

- in HSCT: micafungin 50 mg: CI;
- in acute leukemia: no data;
- caspofungin or anidulafungin: no data.

3.2.6. *Posaconazole*

Following the consensus approval of the first ECIL recommendations on antifungal prophylaxis on October 1st, 2005, results from two additional large (~600 enrolled patients), randomised prophylactic trials have become available. The first study was an open-label but evaluator-blinded study that compared posaconazole oral suspension (200 mg tid) versus standard azole prophylaxis (itraconazole oral suspension 200 mg bid or fluconazole oral solution 400 mg qd) during remission-induction chemotherapy of patients with AML/MDS. The study showed a significant reduction in the number of proven and probable invasive fungal infections (including a significant reduction in the number of *Aspergillus* cases) and demonstrated a statistically significant benefit in overall survival and fungal-free survival in favour of posaconazole.[36] The second study, a double-blind, double-dummy study compared posaconazole oral solution (200 mg tid) versus fluconazole capsules 400 mg qd in allogeneic stem cell transplant recipients with acute or chronic graft-versus-host disease necessitating severe immunosuppressive therapy. In this study posaconazole proved to be non-inferior to fluconazole during the fixed time period of 112 days that was used for the primary end-point analysis. In addition, posaconazole resulted in a significant reduction of the number of proven and probable invasive fungal infections (including *Aspergillus* infections) while on treatment. No survival benefit was seen in this study.[37]

Given the importance of these results but pending the full publication of these studies as well as the in-depth discussion within the next plenary ECIL meeting in 2007, the members of the Working Party and the Chairmen of the prophylaxis session decided to include a *provisional* AI recommendation for posaconazole prophylaxis (200 mg tid) during induction chemotherapy for AML/MDS and during intensive immunosuppressive therapy for acute and chronic GvHD following allogeneic haematopoietic stem cell transplantation.

3.2.7. *Antifungal prophylaxis and changes in fungal epidemiology*

Several reports have pointed out that the use of antifungal prophylaxis has the potential for induction of resistance and results in the selection of natively resistant organisms, potentially leading to a change in the epidemiology of fungal infections. For instance, the use of fluconazole prophylaxis resulted in a ~8-fold increase in the frequency of *Candida glabrata* colonisation and resulted in a shift towards non-albicans *Candida* infections in allogeneic transplant recipients.[35,38] Also, pre-exposure of cancer patients to amphotericin B or triazoles was associated with increased frequency of non-fumigatus *Aspergillus* species. These *Aspergillus* isolates exhibited higher E-test amphotericin B MICs compared with isolates from patients without prior antifungal exposure.[39] Hence, we feel that patients who receive prolonged antifungal prophylaxis should be closely monitored for changes in the colonising fungal flora and in the causative fungal pathogens.

3.2.8. *Duration of antifungal prophylaxis*

In the absence of trials, no firm recommendation regarding the optimal duration of antifungal prophylaxis can be given. However, in neutropenic patients, most experts would agree to continue prophylaxis until recovery of the neutrophil count (ANC > 500/μL) (BIII). In allogeneic transplant recipients, antifungal prophylaxis should probably be continued till day +75

posttransplant (14) or till the end of immunosuppression,[40] whichever comes first (BIII).

4. Conclusion and future prospects

The efficacy of PAC should be assessed in randomised trials, based on an adequate sample size with sufficient statistical power to detect differences between both study arms. These trials should implement uniform and universally accepted criteria of case-definitions and outcome-analysis (incidence of proven candidiasis, incidence of proven and probable aspergillosis, overall mortality and fungal-free survival) and should target high-risk patients only. These objectives can only be achieved by multi-institutional collaboration. Many of the shortcomings in the design of previous studies are or have been addressed in ongoing (e.g. voriconazole versus fluconazole in allogeneic HSCT recipients) or recently closed multicentre studies. Finally, the issue of secondary antifungal prophylaxis (in patients with a previous episode of IFI who are scheduled for a subsequent immunosuppressive or cytotoxic therapy) should also be addressed in prospective clinical trials.

Conflict of interest statement

J.M. has received funds for speaking at symposia organised on behalf of Pfizer, MSD, Schering-plough, Zeneus, and Gilead Science. J.M. is a member of the MSD, Schering-Plough, Zeneus, and Gilead advisory boards for antifungal agents.

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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

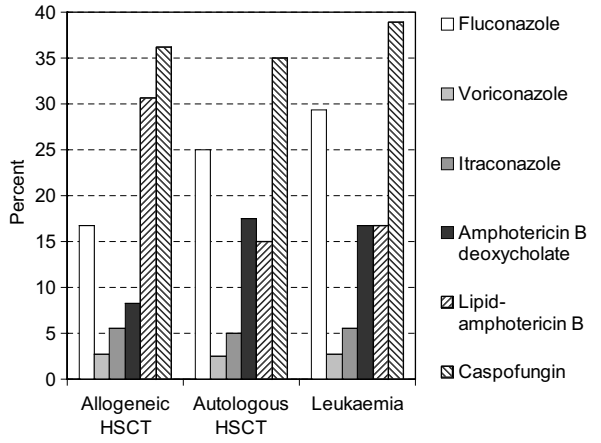

Fig. 1 – Survey on current practice: preferred first line therapy for invasive candidiasis before species identification (38 responses).

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).

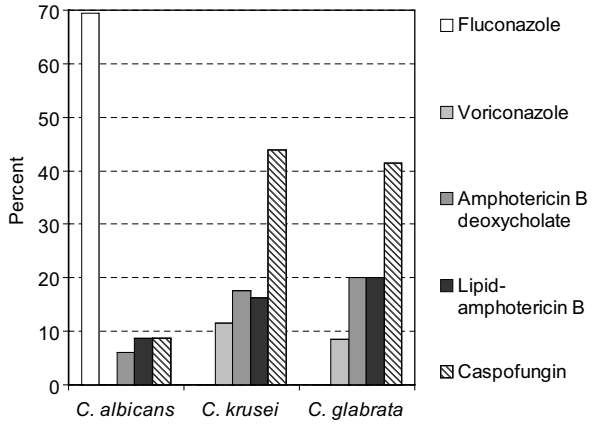

Fig. 2 – Survey on current practice: preferred therapy for invasive candidiasis after species identification (38 responses).

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%).

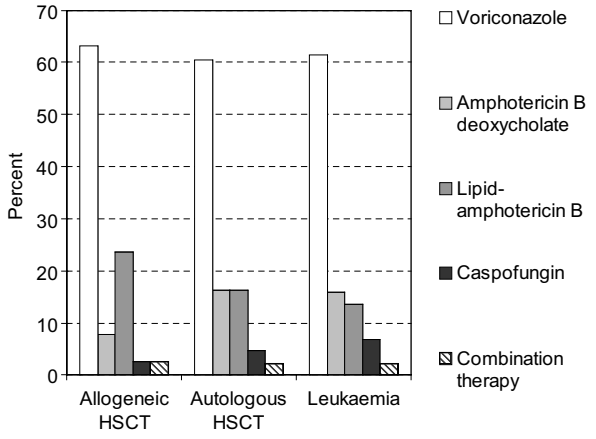

Fig. 3 – Survey on current practice: preferred first line therapy for invasive aspergillosis (38 responses).

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.

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