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Current Perspective

The First European Conference on Infections in Leukaemia – ECIL1: A current perspective

Françoise Meunier[a,*], *Colette Lukan*[b]

[a]*Director General, EORTC, Avenue E. Mounier 83 b11, 1200 Brussels, Belgium*
[b]*Communications Manager, EORTC, Brussels, Belgium*

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ABSTRACT

The First European Conference on Infections in Leukaemia – ECIL1 – was organised under the auspices of the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC), the Infectious Diseases Working Party of the European Group for Blood and Bone Marrow Transplantation (EBMT), the Supportive Care Group of the European LeukaemiaNet (ELN) and the International Immunocompromised Host Society (ICHS). The objective of the meeting was to develop evidence-based guidelines for the management of bacterial and fungal infections in high-risk immunocompromised adult leukaemia patients and hematopoietic stem cell transplantation recipients. The conference was held on September 30th and October 1st, 2005 in Juan-les-Pins, France and brought together a panel of 59 expert haematologists, oncologists, microbiologists, infectious disease specialists and clinical trialists from across Europe, Israel and Australia. The ECIL1 Guidelines were formulated after lengthy discussion, debate and panel consensus on the findings from a relevant comprehensive literature search, results of a European current practice questionnaire and other international guidelines, specific to each of the six clinical areas examined. The final recommendations, published in the Supplements of this journal as a series of six manuscripts in 2007, were well received by the medical community. The ECIL1 organisers anticipated the need for regular review of these guidelines and the Second ECIL Conference was held in September 2007. Publication of the updated and expanded ECIL2 Guidelines is forthcoming. This paper provides a concise summary of the methodology and main recommendations of the ECIL1 Guidelines.

1. Introduction

Guidelines from the First European Conference on Infections in Leukaemia – ECIL1 – for the management of bacterial and fungal infections in high-risk immunocompromised adult leukaemia and hematopoietic stem cell transplantation patients were published one year ago.[1] This collaborative endeavour represents the work of the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC), the Infectious Diseases Working Party of the European Group for Blood and Bone Marrow Transplantation (EBMT), the Supportive Care Group of the European LeukaemiaNet (ELN) and the International Immunocompromised Host Society (ICHS). These guidelines were developed in adherence to strict methodology by an independent network of international experts. Publication of the up-

* *Corresponding author:* Tel.: +32 2 774 16 11; fax: +32 2 774 35 45.
E-mail address: francoise.meunier@eortc.be (F. Meunier).
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dated and expanded ECIL2 guidelines is forthcoming and certain to be equally well received by the medical community.[2] This review provides a concise summary of the main ECIL1 recommendations which should aid clinicians, less involved in clinical research, in their daily practice.

2. Methodology of the ECIL1

The ECIL1 Organising Committee selected six important therapeutic topics for discussion by conference participants. These addressed bacterial and fungal infections in high-risk immunocompromised adult patients: (1) fluoroquinolone prophylaxis for the prevention of bacterial infections, (2) the need for aminoglycosides as part of an initial empirical antibiotic regimen, (3) the need for anti-Gram-positive antibiotics for the treatment of suspected Gram-positive infections, (4) antifungal prophylaxis for the prevention of invasive mycosis, (5) empirical antifungal therapy for persistent fever after broad-spectrum antibiotics and (6) therapy of invasive candidiasis and invasive aspergillosis.

Prior to the Conference, six expert Working Groups each evaluated one topic by means of a comprehensive literature review of articles extracted from Medline, PubMed and/or the Cochrane database published up until September 2005, international guidelines and systematic reviews. Abstracts from the 2002 to 2005 annual meetings of the American Society of Haematology, Interscience Conference on Antimicrobial Agents and Chemotherapy, European Society of Clinical Microbiology and Infectious Diseases, American Society of Clinical Oncology and the European Group for Blood and Marrow Transplantation were screened. Each topic was examined concentrating on overall survival, cause-specific survival, adverse events, development of antimicrobial resistance and cost end-points. Recommendations were formulated and graded for quality of evidence (I–III) and strength of recommendation (A–E) using the Centers for Disease Control system (Table 1).[3] A questionnaire was used to obtain information on current first- and second-line treatment strategies and routine practices in Europe from Conference delegates prior to the meeting.

The Conference was convened on September 30–October 1st, 2005 in Juan-les-Pins, France and attended by 59 experts from 24 European countries, Israel and Australia. Delegates were specialists in haematology, oncology, microbiology, infectious diseases and clinical trials, and selected for their active participation in the host organisations. Each Working Group presented the findings of their literature review, questionnaire analyses and proposed treatment recommendations in plenary session. After initial discussion and debate, each set of recommendations was revised, re-discussed and a final consensus reached on the quality of evidence and grade of each recommendation. Although several pharmaceutical companies provided support for the meeting, their role was limited to that of observer status. The ECIL1 guidelines were published in the European Journal of Cancer Supplements in July 2007.

Table 1 – Centers for disease control grading system for quality of evidence and strength of recommendations[3]

Quality of evidence	Strength of recommendation
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 analytical 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 (i.e. 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

3. Summary of the ECIL1 guidelines on bacterial infections

3.1. *Quinolone prophylaxis in neutropenia*[4]

Fluoroquinolones were assessed for the prevention of bacterial infection in acute leukaemia and hematopoietic stem cell transplantation (HSCT) patients and afebrile neutropenia. An evidence-based literature search identified 780 articles and abstracts with 19 relevant randomised controlled trials and 4 meta-analyses. The final analysis concentrated on two recent large randomised double-blind placebo-controlled trials ($n = 2325$) and one meta-analysis of the remaining 17 trials ($n = 1409$). End-points included febrile episodes requiring empirical antibiotic therapy, bacterial infections and bacteraemia, Gram-negative and Gram-positive infections, all-cause and infection-related mortality. The emergence of resistant bacteria following fluoroquinolone prophylaxis was also evaluated. Most patients had acute leukaemia, whilst five trials evaluated patients with solid tumours or lymphomas. Ciprofloxacin was the most common antibiotic evaluated in addition to norfloxacin, enoxacin, pefloxacin and ofloxacin. Two recent large studies investigated levofloxacin, of which the GIMEMA trial included acute leukaemia and solid tumours/lymphoma patients undergoing HSCT.

3.1.1. *ECIL1 recommendations*

Fluoroquinolone prophylaxis is effective in preventing bacterial infection in acute leukaemia and HSCT recipient afebrile neutropenic patients (IA). The data demonstrate significant reductions in all-cause and infection-related mortality, febrile episodes, bacterial infections (Gram-negative and Gram-positive) and the use of empirical antibiotics. Ciprofloxacin

500 mg twice daily or levofloxacin 500 mg once daily are preferred first choice drugs (IA). Clinicians should monitor for the emergence of fluoroquinolone-resistant bacteria (IIIA) and employ empirical antibiotic therapy active against *Pseudomonas* spp. (IIIA). Fluoroquinolone prophylaxis should commence at the start of chemotherapy and continue until the resolution of the neutropenia or introduction of empirical antibacterial therapy for febrile neutropenia (IIA). Delaying ciprofloxacin prophylaxis until 24–48 h after high-dose cyclophosphamide conditioning prior to allogeneic HSCT or the treatment of non-Hodgkin lymphoma will avoid potential ciprofloxacin-cyclophosphamide interaction (IIIA).

The European practice questionnaire revealed that 61% of respondents utilise antibacterial prophylaxis in neutropenic patients, more in the allogeneic HSCT setting than for acute leukaemia or autologous HSCT. Antibacterial prophylaxis is most commonly initiated to prevent Gram-negative infections, serious infectious complications, bacteraemia, fever and mortality. Ciprofloxacin and levofloxacin are the drugs of choice and the timing of drug initiation and discontinuation mirrored the published data.

3.2. *Aminoglycosides in febrile neutropenia*[5]

The efficacy and safety of aminoglycosides given in combination with β-lactams for the treatment of febrile neutropenia in acute leukaemia or HSCT patients were assessed. An evidence-based literature search identified 805 relevant articles and abstracts. The final analysis included 75 randomised comparative trials of β-lactam monotherapy versus β-lactam-aminoglycoside combination therapy, two meta-analyses, including 66 of the 75 trials ($n \sim 13{,}000$ febrile episodes), 8 randomised comparative trials of once daily versus thrice-daily aminoglycoside therapy, responses from the European practice questionnaire and other international guidelines. End-points included all-cause mortality, treatment failure (death, persistent fever, recurrence or worsening of infection, change of initial antibiotic), toxicity and infection-related mortality.

3.2.1. *ECIL1 recommendations*

β-Lactam monotherapy is as efficacious as and less toxic than β-lactam-aminoglycoside combination therapy with no significant difference observed in all-cause or infection-related mortality, treatment failure or rate of bacterial superinfection (IA). β-Lactam-aminoglycoside therapy is more nephrotoxic and ototoxic than monotherapy (IA). Once daily dosing of aminoglycosides is as efficacious as and less toxic than multiple-dose administration (IA). β-Lactam-aminoglycoside therapy does not prevent the emergence of bacterial resistance compared to β-lactam monotherapy (IB). There is no support for the empirical addition of aminoglycosides to initial β-lactam monotherapy in patients with persistent fever (IIIC) or for documented *Pseudomonas aeruginosa* infections (IIIC). β-Lactam-aminoglycoside combination therapy may be justified for severe sepsis or septic shock (IIIC) and empirically in patients with suspected resistant Gram-negative infections (IIIC).

The European practice questionnaire revealed that almost three-quarters (71%) of experts use initial empirical monotherapy to manage febrile neutropenia favouring pipericillin/tazobactam (21%), meropenem (16%), imipenem (14.5%), cefepime (13.2%) and ceftazidime (7%) as their drug of choice. A third of experts add an aminoglycoside (preferably amikacin) for severe sepsis, suspected *Pseudomonas* or resistant Gram-negative infections, secondary infections or pneumonia.

Other published guidelines are only minimally different from ECIL1. The 2002 Infectious Diseases Society of America Guidelines are consistent with the ECIL1 conclusions regarding the therapeutic equivalence of β-lactam monotherapy and β-lactam-aminoglycoside combination therapy for uncompromised febrile neutropenia.[6] Moreover, additional antibiotics or change in regimen is advised for progression of infection or further complications. No guidance regarding aminoglycoside dosing frequency is given. The 2003 Guidelines of the Infectious Diseases Working Party of the German Society of Haematology and Oncology consider first-line monotherapy and combination therapy to be equivalent for febrile neutropenia and specifically recommend once or thrice-daily amikacin and netilmicin for intermediate-risk patients with persistent fever and neutropenia 6–9 d after initial monotherapy.[7] The 2005 National Comprehensive Cancer Network Guidelines also consider β-lactam monotherapy and combination therapy to be equivalent but recommend a β-lactam-aminoglycoside as first-line therapy for clinically unstable patients or those at high-risk of *P. aeruginosa* infection. Their recommendation for adding aminoglycosides to initial monotherapy is consistent with ECIL1.[8]

3.3. *Glycopeptides in febrile neutropenia*[9]

Empirical first-line anti-Gram-positive antibiotic therapy (i.e. glycopeptides, oxazolidinones or streptogramins) was assessed in neutropenic acute leukaemia patients. An evidence-based literature search identified 44 relevant articles and abstracts with 18 randomised placebo-controlled trials and 2 meta-analyses (including 14 of the 18 trials), which assessed first-line glycopeptide therapy and formed the main dataset. Two randomised controlled trials and one meta-analysis were also reviewed to specifically assess the treatment of neutropenic patients with persistent fever. No randomised placebo-controlled data were available to assess the role of oxazolidinones or streptogramins. End-points included overall and infection-related mortality, success rates with or without antibiotic regimen modification, time to defervescence, breakthrough infections, drug-related nephrotoxicity and skin rash.

3.3.1. *ECIL1 recommendations*

Anti-Gram-positive glycopeptide antibiotics are not indicated for upfront empirical treatment of febrile neutropenia in acute leukaemia patients (ID) or those with persistent febrile neutropenia (ID). Two meta-analyses show that upfront addition of a glycopeptide did not reduce all-cause mortality compared to the other trials, which were all underpowered. Upfront glycopeptide use appeared to be associated with higher treatment success rates, more likely a reflection of study design. The impact of glycopeptides on the risk of breakthrough infections was inconclusive. Most studies and the meta-analyses showed a trend towards increased glycopeptide-induced skin rash and nephrotoxicity. Possible indications for first-line glycopeptide therapy include local predominance of resistant Gram-positive bacteria (i.e.

methicillin-resistant *S. aureus* or penicillin-resistant streptococci), severe sepsis, shock or skin and soft tissue infections including catheter tunnel infections (IIIC). The lack of placebo-controlled data precluded any recommendations for the use of oxazolidinones or streptogramins. The European practice questionnaire showed that almost no expert would give upfront empirical glycopeptide therapy. One half to two thirds would consider anti-Gram-positive therapy for conditions similar to those given by the panel.

4. Summary of the ECIL1 guidelines on fungal infections

4.1. *Empirical antifungal therapy in neutropenia*[10]

Empirical antifungal therapy in acute leukaemia and HSCT patients with neutropenia and persistent fever was assessed. An evidence-based literature search identified 25 comparative trials. Two studies compared empirical Amphotericin B (AmB) deoxycholate to no therapy and 23 trials compared various empirical regimens, 14 of which were excluded for investigating patients with invasive fungal infections at baseline, evaluating toxicity as the primary end-point or being underpowered. Planned end-point analysis included overall response (composite end-point), and resolution of fever, successful treatment of baseline invasive fungal infection (IFI), occurrence of breakthrough IFI, IFI-related mortality, nephrotoxicity, infusion-related events and discontinuations due to adverse events. Additional end-point subgroup analyses included acute leukaemia versus allogeneic or autologous HSCT patients, unexplained versus clinically documented infections and the use of antifungal prophylaxis.

4.1.1. *ECIL1 recommendations*

Empirical antifungal therapy in neutropenic patients with fever persisting 3–7 d following broad-spectrum antibiotics is supported by two studies (1980s) that evaluated AmB deoxycholate. Neither study was, however, sufficiently powered to determine the impact of AmB deoxycholate on IFI morbidity or mortality (IIB). Various antifungal agents have demonstrated equivalent efficacy: liposomal AmB (IA), caspofungin (IA), AmB lipid complex (IB-nephrotoxic in allogeneic HSCT recipients), AmB deoxycholate (IB-not recommended if risk of nephrotoxicity), voriconazole (IB-first choice for aspergillosis, less effective than liposomal AmB), itraconazole (IC-tolerance concerns) and fluconazole (IC-emergence of *Candida* resistance, inactive against *Aspergillus*). No recommendations can be offered for selecting specific antifungals based on underlying condition, previous antifungal therapy or known infection source as no individual antifungal showed clear superiority.

The European practice questionnaire revealed that 97% of respondents consider empirical antifungal therapy a standard practice and initiate therapy within a median of 5 d for the first febrile episode and 3 d for relapsing fever. Antifungal therapy should be delayed (6.5 d) for microbiologically documented bacterial infection (50%). AmB deoxycholate is the first choice for acute leukaemia or autologous HSCT patients undergoing induction or consolidation chemotherapy, whilst liposomal AmB is preferred for allogeneic HSCT recipients. AmB deoxycholate is preferred for unexplained fever; caspofungin or fluconazole for enterocolitis/gastroenteritis *Candida* colonisation; voriconazole for lung infiltrates and/or a positive serum galactomannan test; and liposomal amphotericin B or caspofungin for clinically unstable patients.

4.2. *Primary antifungal prophylaxis in leukaemia patients*[11]

Primary antifungal chemoprophylaxis (PAC) in acute leukaemia, high-risk myelodysplastic syndrome and allogeneic HSCT patients was assessed. An evidence-based literature search identified 40 publications and abstracts of which 21 controlled trials and 3 meta-analyses were reviewed. Planned end-points included reduction in the number of proven or probable invasive fungal infections (IFI), improvement in fungal-free survival and overall survival. However, because these were not consistently evaluated, surrogate end-points were used (impact on persistent fever, frequency of IFI, use of empirical antifungal therapy and IFI-related mortality), in addition to toxicity, tolerability, drug interactions, patient compliance and quality of life.

4.2.1. *ECIL1 recommendations*

In patients undergoing allogeneic HSCT, primary antifungal chemoprophylaxis with fluconazole 400 mg/d i.v./oral (IA) and itraconazole 200 mg i.v. followed by oral solution 200 mg b.i.d. (IB) with appropriate drug level monitoring (IIB) are recommended. Oral posaconazole (200 mg t.i.d.) is indicated during intensive immunosuppressive therapy for acute and chronic graft-versus-host disease following HSCT (IA) and induction chemotherapy for acute leukaemia or myelodysplastic syndrome (IA-*provisional*). The use of fluconazole 50–400 mg/d i.v./oral (IC), itraconazole oral solution 2.5 mg/kg b.i.d. (IC), lipid AmB deoxycholate (IC) and systemic low-dose AmB deoxycholate (IIC) are considered options in acute leukaemia and autologous HSCT patients. Prolonged antifungal prophylaxis may induce resistance. Close monitoring for changes in colonising fungal flora and causative fungal pathogens is required. In neutropenic patients, prophylaxis should continue until the absolute neutrophil count exceeds 500/μL (IIIB), whereas in allogeneic HSCT patients, treatment should continue until 75+ days post-transplant or until the end of immunosuppression (IIIB).

The practice questionnaire revealed that 87% of experts employ prophylactic antifungal therapy: 85% for allogeneic HSCT versus 63% in autologous HSCT or acute leukaemia patients. Fluconazole was the antifungal of first choice (~55%) followed by itraconazole (oral solution) and non-absorbable AmB. The duration of therapy was variable and dependent on clinical setting.

4.3. *Treatment of invasive Candida and invasive Aspergillus infections*[12]

Antifungal therapy in adult patients with acute leukaemia or HSCT and invasive candidiasis or invasive aspergillosis was assessed. End-points included optimal first- and second-line treatment(s), optimal duration of therapy, current indications for candidemia and aspergillosis infection and the role of

in vitro susceptibility testing. An evidence-based literature search identified 84 articles and abstracts from which 12 randomised first-line trials were reviewed: 8 in invasive candidiasis or candidemia and neutropenia ($n = 3319$) and 4 evaluating invasive aspergillosis ($n = 593$).

4.3.1. *ECIL1 recommendations*

Recommendations for the treatment of invasive candidiasis are based on an overall study population ($n = 3319$) and a subgroup with hematologic malignancies and neutropenia ($n = 306$). In the non-neutropenic patient and prior to species isolation, fluconazole, AmB deoxycholate, caspofungin and voriconazole are equally effective (IA), noting that AmB deoxycholate is not generally recommended when concomitant nephrotoxic drugs are used (IIID) and should not be given if renal insufficiency exists (IIIE). Anidulafungin (IA) and micafungin (IIA) are provisionally recommended based on published studies made available after the ECIL1 meeting. In the subgroup of hematologic neutropenic patients studied, lipid AmB, caspofungin and voriconazole are generally recommended (IIB) in the absence of species identification, and caution is advised when using fluconazole due to prior use in prophylaxis and the emergence of non-*albican* strains in this patient subset. Caspofungin is the drug of choice (IIB) for documented *C. albicans*, *C. galabrata* or *C. krusei* infections. Central venous line catheter removal is recommended for non-hematologic (IIA) as well as for neutropenic or leukaemia patients (IIIB) with candidaemia and strongly recommended if *C. parapsilosis* is isolated (IIA). Treatment in non-neutropenic patients should continue for 14 d after the last positive blood culture and resolution of signs and symptoms (IIIB). In neutropenic patients, resolution of the neutropenia is also a treatment end-point.

Primary therapy with voriconazole is strongly recommended for pulmonary invasive aspergillosis in adult haematologic patients (IA) as well as extra-pulmonary infections (i.e. central nervous system) based on efficacy, safety and survival data. Liposomal AmB (*provisional* IB) and AmB lipid complex (IIB) are alternatives to voriconazole which is contra-indicated in renal insufficiency. Data supporting the use of caspofungin and itraconazole (both IIIC) were insufficient. AmB colloid dispersion and AmB deoxycholate (both ID) were not generally recommended. Options for salvage therapy include caspofungin, posaconazole or voriconazole (all IIB) depending on the agent used for primary therapy.

Caspofungin-lipidAmB and caspofungin–voriconazole (both IIIC) are options for combination salvage therapy. Anti-aspergillosis therapy should continue until complete response and resolution of the immunocompromised state. Routine *Aspergillus* susceptibility testing is not recommended; however, species level identification can guide therapeutic choices (IIIC). Surgical management should be considered on an individual basis, for pulmonary lesions in close proximity to large vessels or haemoptysis.

Approximately 40% of respondents to the European practice questionnaire prescribe caspofungin for first-line treatment of invasive candidiasis prior to species identification in allogeneic and autologous HSCT and acute leukaemia patients, whereas fluconazole was the second most preferred. Moreover, 31% of experts favour liposomal AmB in allogeneic HSCT patients to AmB deoxycholate. Both are employed for autologous HSCT and leukaemia patients. Fluconazole is used when *C. albicans* is isolated (69%) and caspofungin for *C. galabrata* and *C. krusei* (40%). Voriconazole is the preferred first-line agent for invasive aspergillosis (>60%), followed by lipid-based AmB for allogeneic HSCT patients and lipid-based AmB or AmB deoxycholate equally for autologous HSCT and leukaemia patients. Combination therapy is reserved for central nervous system infections, extensive pulmonary and other disseminated infections: voriconazole-caspofungin (45%), caspofungin-liposomal AmB (39%) and voriconazole-liposomalAmB (24%). Caspofungin, voriconazole and liposomal AmB are used for second-line monotherapy.

5. Future perspectives

The past 20 years have witnessed tremendous progress in the management of cancer-related infections. Numerous questions remain. Despite dramatic decreases in mortality, optimal prevention and treatment strategies must be re-evaluated in light of changes in treatment of the underlying diseases, use of oral agents, ambulatory treatment practices and the costs of newly developed drugs. These issues will be addressed within the ECIL framework with continued participation of the EORTC network to ensure that all clinicians have up-to-date information, expert opinions and recommendations to provide the best patient care.

Conflict of interest statement

None declared.

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