# The use and efficacy of empirical *versus* pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project

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## ABSTRACT

### Background
Neutropenic patients with persistent fever despite antibiotic therapy are managed with empirical or pre-emptive antifungal therapy. The aim of the present study was to evaluate the current clinical use and efficacy of these two approaches in patients with high risk hematologic conditions.

### Design and Methods
An electronic medical record system, the "Hema e-Chart", was designed and implemented to collect information prospectively on infectious complications, particularly on invasive fungal diseases, in patients with hematologic malignancies treated with chemotherapy and/or autologous or allogenic hemopoietic stem cell transplantation. The patients were enrolled from Hematology units distributed widely across Italy.

### Results
Three hundred and ninety-seven adults with hematologic malignancies treated with chemotherapy with persistent fever and suspected invasive fungal disease were evaluable for the study (190 treated had been treated with empirical antifungal therapy and 207 with pre-emptive antifungal therapy). There was a significantly lower incidence of proven/probable invasive fungal diseases in patients treated with empirical antifungal therapy (n=14, 7.4%) than in patients treated with pre-emptive therapy (n=49, 23.7%) ($P$<0.001). The rate of deaths attributable to invasive fungal diseases was significantly lower in subjects treated with empirical antifungal therapy (1 case; 7.1%) than in subjects treated with pre-emptive therapy (11 cases; 22.5%) ($P$=0.002).

### Conclusions
These data indicate that empirical antifungal treatment decreased the incidence of invasive fungal disease and of attributable mortality with respect to a pre-emptive antifungal approach in neutropenic febrile patients with hematologic malignancies. *(ClinicalTrials.gov Identifier: NCT01069887)*

Key words: empirical antifungal therapy, pre-emptive antifungal therapy, hematologic malignancies.

*Citation: Pagano L, Caira M, Nosari A, Cattaneo C, Fanci R, Bonini A, Vianelli N, Garzia MG, Mancinelli M, Tosti ME, Tumbarello M, Viale P, Aversa F, and Rossi G on behalf of the HEMA e-CHART Group, Italy. The use and efficacy of empirical* versus *pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project. Haematologica 2011;96(9):1366-1370. doi:10.3324/haematol.2011.042598*



*Acknowledgments: this project was supported by an unrestricted grant from Merck & Co, Italy. The authors gratefully acknowledge the many dedicated coordinators who ultimately made this project a success.*

*Manuscript received on February 17, 2011. Revised version arrived on May 3, 2011. Manuscript accepted May 5, 2011.*

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## Introduction

Invasive fungal diseases are a leading cause of death in severely neutropenic patients who, consequently, need early and effective treatment.[1] The best therapeutic approach for patients with suspected invasive fungal disease is, however, still debated. The *empirical approach* is frequently recommended in high-risk patients, in order to guarantee early treatment.[2,3] The *pre-emptive approach* is a logical alternative to empirical therapy, with the aim of targeting antifungal therapy better and avoiding over-treatment.

Although various studies have compared these two different strategies, using several diagnostic criteria for starting the pre-emptive approach,[4-7] the lack of controlled trials does not allow conclusions to be drawn on their advantages and critical issues.

The aim of this study was to evaluate the impact of empirical *versus* pre-emptive antifungal therapy on the clinical outcome of neutropenic, high-risk hematologic patients in current clinical practice.

## Design and Methods

From March 2007 to March 2009, each patient with a newly diagnosed hematologic malignancy who received conventional chemotherapy in any of 23 Italian Hematology Units was consecutively registered in the Hema e-Chart registry and followed up. The hematologic malignancies were acute and chronic leukemia (myeloid and lymphoid), Hodgkin's and non-Hodgkin's lymphomas, myelodysplastic syndromes, chronic myeloproliferative disorders, and multiple myeloma. Data were entered prospectively into electronic case report forms using methods already described.[8] Registered data were managed in accordance with the Italian Data Protection (Privacy) law. The use of the Hema e-Chart registry was approved by the Ethics Committee of each participating site.

Given the non-interventional type of study, enrolling a patient in the Hema e-Chart registry had no impact on the standard clinical practice of each Hematology Unit. However, the diagnostic work-up was almost identical in all of the participating centers: blood cultures at the onset of fever, to be repeated successively if negative, followed by nasal, pharyngeal and rectal swabs; serological tests for invasive fungal disease; and computed tomography (CT) scans on the 4-7$^{th}$ day of fever. Additional investigations, such as abdominal ultrasound, sinus or brain CT scan, skin biopsy, bronchoalveolar lavage or fundoscopy, were performed according to patients' symptoms. The last patient was enrolled on March 31$^{st}$, 2009 and followed-up until June 30$^{th}$, 2009.

For each patient who experienced a febrile event, main baseline information was requested (i.e. age, gender, disease, stage, and date of latest anti-cancer therapy). The clinical record of the febrile event was then started and updated every 3 days. The case report form included information about clinical data (fever and main symptoms); current risk factors (e.g. central venous catheter, parenteral nutrition, level and duration of neutropenia); concomitant therapy (e.g. antibiotics, steroids, antiviral); anti-fungal prophylaxis (primary *versus* secondary, administered drug); laboratory data (e.g. liver and renal function parameters). Specific information about the febrile episode referred to the diagnostic work-up (microbiological data, CT scan, X-ray, broncho-alveolar lavage, histology, etc.) and to the antifungal therapy (drugs employed, dosage).

All clinical and laboratory data were registered consecutively for each patient. After conclusion of the event, the investigator completed the case report form by specifying the diagnosis and selecting one or more of the following options: bacterial infection, viral infection, fungal infection, fever of unknown origin, fever due to non-infectious causes and also describing the outcome.

All invasive fungal diseases diagnosed were centrally reviewed by the Scientific Advisory Board and classified in accordance with the new 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria.[9]

We considered an *empirical approach* to be administration of an antifungal agent to a neutropenic patients with persistent fever without a known source of infection and unresponsive to appropriate antibacterial agents. The *pre-emptive approach* consisted of the administration of an antifungal agent to patients with laboratory tests or radiographic signs indicative of invasive fungal disease, without definitive proof from histopathology or cultures in an appropriate clinical subset. This subset of patients included those with fever and multisite colonization (colonization of multiple, non-contiguous body sites) by *Candida* species.[10,11]

Mortality was considered due to invasive fungal disease when patients died within 12 weeks of the onset of fever with microbiological, histological, or clinical evidence of active infection, and if other potential causes of death could be excluded by the physician responsible for the patient.[12] Results from autopsy, if performed, were required. All cases were reviewed by the Scientific Advisory Board, which genereted queries for those cases in which the cause of death appeared to be less clear. At the end of the data review, the rate of agreement between the Scientific Advisory Board members was 100%.

Student's t-test was used to investigate the significance of differences in continuous variables between groups. Pearson's $\chi^2$-test and Fisher's exact test were used, when appropriate, to evaluate differences in discrete characteristics between groups. The Kaplan-Meier method was used for the survival analysis. *P* values were considered statistically significant when less than 0.05.

We report here part of the results developed by the Hema e-Chart registry concerning the diagnosis and therapy of invasive fungal diseases.

## Results

Over a 24-month period, 397 adults with high-risk hematologic diseases received antifungal treatment for at least 7 days for persistent fever and suspected invasive fungal disease and were considered evaluable for this study; 190 (47.9%) of them had been treated with empirical antifungal therapy, while 207 (52.1%) had received pre-emptive treatment. The baseline characteristics of the patients enrolled are shown in Table 1.

The majority of patients in both groups suffered from acute leukemia (myeloid or lymphoid), and more than 90% of them were profoundly neutropenic (neutrophil count $<0.5\times10^9$/L) at the onset of fever. The mean age of patients given empirical antifungal therapy was significantly lower than that of patients given pre-emptive antifungal therapy ($P<0.001$).

Comparing the two groups, a significantly higher number of patients in the empirically treated group had received first induction chemotherapy for the underlying malignancy ($P<0.001$). As expected, the duration of fever before starting antifungal treatment was significantly shorter in those patients treated with the pre-emptive approach ($P=0.001$). A significant difference in antifungal prophylaxis was found, as this was more frequently administered in the pre-emptively treated group ($P=0.05$), while there were no differences in the duration of prophylaxis.

As regards the antifungal treatment, fluconazole was

more frequently prescribed in the empirically treated group, while voriconazole was more often used in the pre-emptive group; treatments with amphotericin B compounds and caspofungin were equally distributed in the two groups. The mean duration of antifungal treatment was significantly shorter in patients treated empirically than in those treated with a pre-emptive approach ($P$=0.001) (Table 1).

There were no significant differences between the two groups for any of the baseline parameters examined (sex, underlying malignancy, phase of disease, neutropenia duration and recovery, agent used in prophylaxis, and duration of prophylaxis) (Table 1).

The number of detected proven/probable invasive fungal diseases was significantly lower in patients treated with empirical antifungal therapy (n=14, 7.4%; 9 proven invasive fungal diseases and 5 probable ones) than in those treated with pre-emptive antifungal therapy (n=49, 23.7%; 16 proven invasive fungal diseases and 33 probable ones) ($P$<0.001).

As far as concerns the causative pathogens, the number of isolated yeasts was similar in the two groups (7 strains in the empirical group and 12 strains in the pre-emptive group) but the number of isolated molds was higher in the pre-emptive group (37 *versus* 7) (Table 1). All yeasts were isolated from blood samples, while molds were isolated from the respiratory tract. In the majority of cases the pre-emptive antifungal approach was driven by a positive CT-scan (161 patients, 78%), while remaining patients had a positive galactomannan test (34 patients, 16%). All 12 patients with a yeast infection (6%) had developed fever in the context of multisite colonization. None of our patients experienced any breakthrough infection while on antifungal empirical/pre-emptive treatment. In contrast, nearly half of the patients with invasive fungal diseases developed their infection while on antifungal prophylaxis. Most of the yeast infections (16/19, 68%) occurred in patients who had not received any systemic prophylaxis.

The overall and invasive fungal disease-attributable mortality rates were significantly lower in patients treated with empirical therapy (6.3 and 7.1%, respectively) than in those treated with pre-emptive antifungal therapy (15.9 and 22.5%, respectively) (Table 1). Autopsy was not routinely performed in all patients who died. Information was available for five of 12 patients who died of invasive fungal disease (42%) and in all these cases the invasive fungal disease was confirmed to have been the cause of death. As shown in Figure 1, the overall survival rate at day 90 was significantly higher among patients treated with an empirical approach (Figure 1A).

A specific subgroup analysis of patients with acute myeloid leukemia who received first-line induction chemotherapy confirmed the higher incidence rate of invasive fungal diseases and the lower probability of survival (Figure 1B) in the pre-emptively treated patients. In contrast, there was no significant difference in mortality attributable to invasive fungal diseases.

The results of the univariate and multivariate analyses of risk factors for mortality are reported in Table 2. At univariate analysis outcome was negatively influenced by age, while the empirical approach had a positive influence on outcome. The outcome of the infection was not influenced by the etiology (yeasts *versus* molds). Age and empirical antifungal approach remained statistically significant also at multivariate analysis.

## Discussion

Empirical antifungal therapy in neutropenic febrile patients was introduced in the early 1980s because of the high incidence of invasive fungal diseases, high mortality rate, low sensitivity of cultures, late diagnosis of fungal infections and consequent low success rates of delayed treatment.[13] The aim of this strategy is to treat suspected fungal infections as early as possible in order to achieve the best results.[14] The drawback of the strategy is that about 40-50% of neutropenic patients with fever who do not respond to broad-spectrum antibiotics are candidates for empirical

**Table 1. Comparison between empirical and pre-emptive treatment groups: principal demographic characteristics and clinical outcomes in 397 registered patients.**

| Variable | Empirical n=190 (%) | Pre-emptive n=207 (%) | *P* value |
|---|---|---|---|
| Age, years (range) | 52.3 (14-83) | 58.1 (18-84) | <0.001 |
| Sex (female/male) | 89/101 | 79/128 | 0.08 |
| Underlying malignancy (%) | | | |
| Acute myeloid leukemia | 152 (80) | 169 (81.6) | 0.67 |
| Non-Hodgkin's lymphoma | 16 (8.4) | 14 (6.8) | 0.53 |
| Acute lymphoblastic leukemia | 11 (5.8) | 14 (6.8) | 0.68 |
| Multiple myeloma | 3 (1.6) | 3 (1.5) | 0.91 |
| Myelodysplastic syndrome | 3 (1.6) | 4 (1.9) | 0.78 |
| Chronic lymphocytic leukemia | 2 (1.1) | 1 (0.5) | 0.51 |
| Hodgkin's lymphoma | 2 (1.1) | 1 (0.5) | 0.51 |
| Chronic lyeloid leukemia | 1 (0.5) | 1 (0.5) | 0.95 |
| Phase of treatment, n (%) | | | |
| Consolidation | 6 (3.1) | 3 (1.4) | 0.25 |
| First line | 155 (81.6) | 147 (71) | 0.01 |
| Second line/salvage therapy | 29 (15.3) | 57 (27.5) | 0.003 |
| Profound neutropenia (%) | 174 (91.6) | 192 (92.8) | 0.6 |
| Neutrophil recovery (%) | 120 (63.2) | 133 (64.3) | 0.9 |
| Prophylaxis (%) | 93 (48.9) | 121 (58.5) | 0.05 |
| Kind of prophylaxis, n. (%) | | | |
| Itraconazole | 48 (51.6) | 60 (49.6) | 0.40 |
| Fluconazole | 36 (38.7) | 47 (38.8) | 0.35 |
| Posaconazole | 7 (7.5) | 9 (7.4) | 0.73 |
| Other | 2 (1) | 5 (2.4) | 0.30 |
| Prophylaxis duration, mean days (SD) | 8.3 (8.2) | 8.3 (6.6) | 0.9 |
| Previous fever duration, mean days (SD) | 5.4 (5.1) | 7.3 (6.6) | 0.001 |
| Drugs, n (%) | | | |
| Amphotericin B compounds | 68 (35.8) | 78 (38.6) | 0.69 |
| Fluconazole | 49 (25.8) | 8 (3.9) | <0.001 |
| Caspofungin | 47 (24.7) | 68 (32.9) | 0.07 |
| Voriconazole | 18 (9.5) | 42 (20.3) | 0.002 |
| Combinations | 3 (1.6) | 4 (1.9) | 0.78 |
| Others | 5 (2.6) | 7 (2.4) | 0.66 |
| Mean duration of antifungal treatment, days (SD) | 8.7 (6.2) | 11.2 (8.4) | 0.001 |
| Proven/probable IFD n. (%) | 14 (7.4%)<br>• 7 molds<br>• 7 yeasts | 49 (23.7%)<br>• 37 molds<br>• 12 yeasts | <0.001 |
| Death in patients with IFD | 1<br>• 1 yeast[1] | 11<br>• 8 molds[2]<br>• 3 yeasts[3] | 0.002 |
| IFD-attributable mortality (%) | 1/14 (7.1) | 11/49 (22.5) | 0.002 |
| Overall 90-day mortality (%) | 12/190 (6.3) | 33/207 (15.9) | 0.002 |

*SD: standard deviation; IFD: invasive fungal disease.[1] 1 Histoplasma; [2] 8 Aspergillus spp; [3] 2 Candida spp, 1 Trichosporon.*

antifungal therapy, while the incidence of invasive fungal diseases in this category is only about 10-15%. Several therapeutic schemes using amphotericin B (deoxycholate and lipid compounds), azoles or echinocandins have been compared as the empirically administered drug over the years, but none of them showed significant advantages in terms of reducing proven/probable invasive fungal diseases.[15-17] In contrast, the proportion of patients successfully treated with an empirical approach seems to have decreased over the last few years;[16,17] as a consequence many doubts have been raised about the real benefits of this approach. The empirical approach has also been challenged because of the availability of new non-invasive diagnostic techniques (i.e. galactomannan, β-D-glucan) which allow clinicians to anticipate the diagnosis and to avoid unnecessary treatment.

In 2005, Maertens *et al.* first evaluated the feasibility of a "pre-emptive" approach based on the incorporation of sensitive, non-invasive diagnostic tests (galactomannan and CT-scanning) for high-risk neutropenic patients who had received fluconazole prophylaxis while avoiding empirical therapy.[5] This approach reduced the rate of antifungal use for febrile neutropenia from 35% to 7.7%, lowering the exposure to expensive and potentially toxic drugs, and led to the early initiation of antifungal therapy in about 7% of episodes that had not been clinically suspected of being related to an invasive fungal disease. Other more recent studies compared polymerase chain reaction- or galactomannan-based approaches to the empirical one, but none of them was found to be more advantageous.[6,7] A recent study by Girmenia *et al.* assessed the feasibility of an intensive clinically-driven diagnostic strategy based on galactomannan tests and CT-scans in selected patients with neutropenic fever. This strategy was able reduce the use of antifungal treatment by 43% compared to that used with a standard empirical approach. At the 3-month follow-up, 63% of the patient with invasive fungal disease had survived, and no cases of undetected invasive fungal disease were found. The authors suggested that this diagnostic approach can ensure effective antifungal control and reduce exposure to unnecessary antifungal treatment.[18]

In a multicenter, open-label, randomized study, Cordonier *et al.* directly compared empirical *versus* pre-emptive antifungal therapy using amphotericin B compounds for high-risk, febrile, neutropenic patients.[18] In their study probable and proven invasive fungal diseases were more common among patients who received pre-emptive treatment (13/143 *versus* 4/150; $P<0.05$); the overall survival rate was equivalent in the two groups (97.3% in the empirical treatment group and 95.1% in the pre-emptive treatment group). The authors concluded that a pre-emptive strategy did not affect overall survival while it did decrease the use of antifungal drugs compared to the use with a classical empirical approach.[4]

Of note, given the lack of a standard definition for a "pre-

**Table 2.** Predictors of mortality in the 397 registered patients.

| Variable | N. (%)of patients | | | |
|---|---|---|---|---|
| | Dead (n=45) | Survivors (n=352) | *P* value | OR (95% CI) |
| **Univariate analysis** | | | | |
| Demographic information | | | | |
| Male sex | 29 (64.4) | 200 (56.8) | 0.32 | 1.37 (0.69-2.81) |
| Age (year [mean SD]) | 62±10 | 54±16 | <0.001 | |
| Hematologic malignancy | | | | |
| Acute myeloid leukemia | 34 (75.5) | 287 (81.5) | 0.33 | 0.70 (0.32-1.61) |
| Chronic myeloid leukemia | 0 | 2 (0.6) | 1 | 0 (0-15.25) |
| Acute lymphocytic leukemia | 4 (8.9) | 21 (5.9) | 0.50 | 1.53 (0.36-4.87) |
| Chronic lymphocytic leukemia | 1 (2.2) | 2 (0.6) | 0.30 | 3.97 (0.06-77.42) |
| Non-Hodgkin's lymphoma | 6 (13.3) | 24 (6.8) | 0.13 | 2.10 (0.66-5.70) |
| Hodgkin's lymphoma | 0 | 3 (0.8) | 1 | 0 (0-10.16) |
| Multiple myeloma | 0 | 6 (1.7) | 1 | 0 (0-5.03) |
| Myelodysplastic syndromes | 0 | 7 (1.9) | 1 | 0 (0-4.29) |
| Clinical presentation | | | | |
| Central venous catheter | 21 (46.7) | 180 (51.1) | 0.57 | 0.83 (0.42-1.63) |
| Neutropenia (PMN<0.5×10⁹/L) | 40 (88.9) | 326 (92.6) | 0.38 | 0.63 (0.22-2.25) |
| Antifungal prophylaxis | 20 (44.4) | 194 (55.1) | 0.17 | 0.65 (0.33-1.27) |
| Steroid use | 6 (13.3) | 27 (7.6) | 0.19 | 1.85 (0.58-4.95) |
| Positive lung X-ray | 15 (33.3) | 82 (23.3) | 0.14 | 1.64 (0.78-3.33) |
| Positive lung CT-scan | 24 (53.3) | 162 (46) | 0.35 | 1.24 (0.68-2.63) |
| Etiology and treatment | | | | |
| Yeast | 4 (8.9) | 15 (4.3) | 0.17 | 2.19 (0.50-7.31) |
| Molds | 8 (17.8) | 36 (10.2) | 0.13 | 1.89 (0.71-4.55) |
| Empirical antifungal treatment | 12 (26.7) | 178 (50.6) | 0.002 | 0.35 (0.16-0.73) |
| **Multivariate analysis** | | | | |
| Age (year [mean SD]) | | | 0.006 | 1.03 (1.01-1.06) |
| Empirical antifungal treatment | | | 0.01 | 0.40 (0.20-0.82) |

*SD: standard deviation; OR: odd's ratio; PMN: polymorphonuclear cells.*

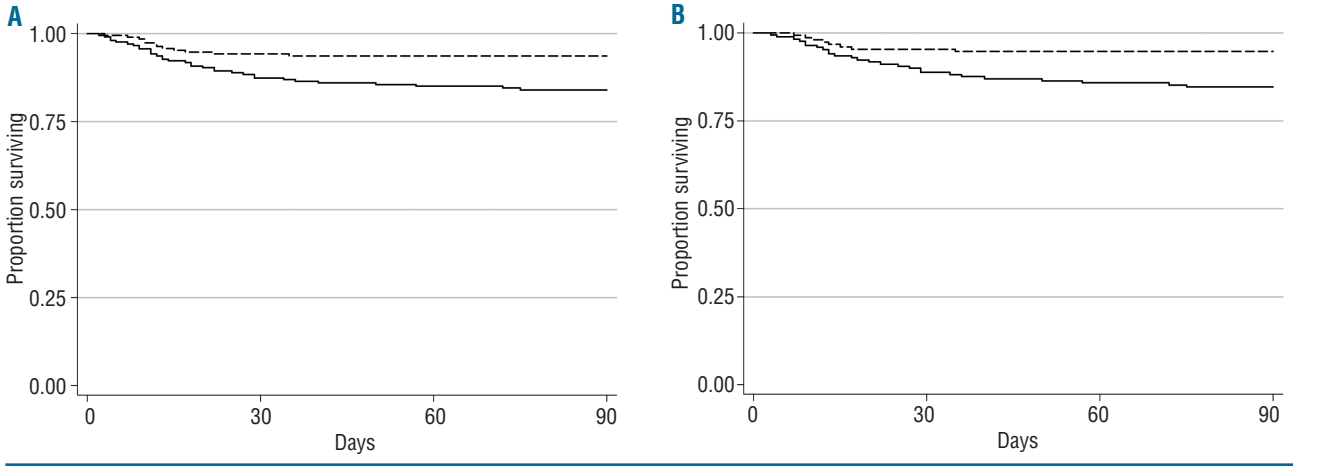


**Figure 1.** Kaplan-Meier curves showing the impact of empirical (*dotted line*) *versus* pre-emptive (*solid line*) therapy on 90-day mortality in all 397 patients (A), and in the subgroup of 321 patients with AML at first line of treatment (B). *P*=0.002 for both A and B.

emptive approach", the variability of available data and the possible excess of risk in those treated with this strategy, recently published guidelines decided not to grade a recommendation for this approach.[19]

In our study we analyzed the results of the empirical and pre-emptive strategies in a real life clinical setting. The number of patients receiving each approach was almost identical, but some clinical and epidemiological differences emerged between the two groups. It could be speculated that previous administration of systemic antifungal prophylaxis may influence the choice of later treatment. Interestingly, the possible benefits of delayed therapy in terms of less toxicity seemed to disappear in our series, since patients treated with the pre-emptive approach required longer treatment. The mean age of patients in the empirical group was lower, probably because physicians tend to avoid risks in younger patients and to start antifungal treatment even if clinical evidence is poor. The consequent over-treatment with empirical antifungal therapy did not have a clinical impact on the patients thanks to the lower toxicity of the new antifungal drugs.

Like Cordonnier *et al.*, we registered a lower incidence of invasive fungal disease in the empirically treated group. Additionally in our series empirical therapy was able to reduce the invasive fungal disease-attributable mortality and to increase survival probability of patients when compared to the pre-emptive approach. The analysis of the subgroup of patients with acute myeloid leukemia in first induction showed a lower incidence of invasive fungal disease as well as a higher survival rate in the empirically treated group.

The favorable impact of the empirical approach on mortality emerged from both univariate and multivariate analyses. Of course these results need further validation, as they may be influenced by many factors, such as the type of study (observational, not randomized), the inclusion of patients possibly not suffering from an invasive fungal disease in the empirically treated group, and some epidemiological differences between the two study groups (empirical *versus* pre-emptive).

Of note in this registry, 25% of patients received fluconazole as empirical treatment; this may be because almost none of these patients had received prior prophylaxis and had evidence of yeast colonization.

Despite the risk of overtreatment in patients who do not have an invasive fungal disease, the empirical approach seems able to guarantee a better outcome in hematologic patients, probably making it the best choice when adequate microbiological and radiological support is lacking. Pre-emptive therapy should be reserved to those centers in which a risk-based approach is feasible, using clinical rules and intensive diagnostic techniques to identify patients with invasive fungal disease at a very early stage of disease.[20]

## Authorship and Disclosures

*The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.*

*Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.*

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