Universal antifungal therapy is not needed in persistent febrile neutropenia: a tailored diagnostic and therapeutic approach

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ABSTRACT

Background
Giving antifungal therapy exclusively to selected patients with persistent febrile neutropenia may avoid over-treatment without increasing mortality. The aim of this study was to validate an innovative diagnostic and therapeutic approach based on assessing patients' risk profile and clinical criteria in order to select those patients requiring antifungal therapy. The efficacy of this approach was compared to that of universal empirical antifungal therapy.

Design and Methods
This was a prospective study which included all consecutive adult hematology patients with neutropenia and fever refractory to 5 days of empirical antibacterial therapy admitted to a teaching hospital in Spain over a 2-year period. A diagnostic and therapeutic approach based on clinical criteria and risk profile was applied in order to select patients for antifungal therapy. The sensitivity, specificity and negative predictive value of this approach and also the overall success rate, according to the same criteria of efficacy described in classical clinical trials, were analyzed.

Results
Eighty-five episodes were included, 35 of them (41.2%) in patients at high risk of invasive fungal infections. Antifungal therapy was not indicated in 33 episodes (38.8%). The overall incidence of proven and probable invasive fungal infections was 14.1%, all of which occurred in patients who had received empirical antifungal therapy. The 30-day crude mortality rate was 15.3% and the invasive fungal infection-related mortality rate was 2.8% (2/72). The overall success rate following the diagnostic and therapeutic approach was 36.5% compared with 33.9% and 33.7% obtained in the trial by Walsh *et al.* The sensitivity, specificity and negative predictive value of the study approach were 100%, 52.4% and 100%, respectively.

Conclusions
Based on the high negative predictive value of this diagnostic and therapeutic approach in persistent febrile neutropenia patients with hematologic malignancies or patients who have received a hematopoietic stem cell transplant, the approach is useful for identifying patients who are not likely to develop invasive fungal infection and do not, therefore, require antifungal therapy. The effectiveness of the strategy is similar to that of universal empirical antifungal therapy reported in controlled trials.

Key words: persistent febrile neutropenia, invasive fungal infection, selective antifugal therapy, empirical antifugal therapy.

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The online version of this article has a Supplementary Appendix.

Introduction

Invasive fungal infection (IFI) is a major cause of mortality among patients with hematologic malignancies and hematopoietic stem cell transplant (HSCT) recipients.[1] Its incidence has increased over the past years,[2-4] often resulting in limitations to chemotherapy administration and worsening the prognosis of patients with hematologic diseases. Since the main risk factor for IFI in these patients is profound and prolonged neutropenia, universal empirical antifungal therapy in neutropenic patients after 5-7 days of persistent fever has been recommended by the Infectious Diseases Society of America (IDSA)[5] over the last two decades even though the scientific evidence supporting this standard of care is weak[6] and the strategy has important drawbacks such as toxicity, increased cost and risk of antifungal resistance.[7-9] In recent years, some authors have suggested that limiting antifungal therapy to selected patients may avoid over-treatment without increasing IFI-related mortality,[10-14] but it would be desirable to design a feasible, effective and safe approach for selecting patients for the antifungal therapy. Moreover, this approach has not been evaluated in patients at the highest risk of IFI such as allogeneic HSCT recipients.

Cisneros *et al.*[12] proposed an approach for selecting patients for antifungal therapy based on risk profile and driven by clinical criteria;[12] the efficacy and safety of this approach were established in a pilot study conducted in our center.[10] Those results were limited by the non-routine determination of serum galactomannan antigen (GM) and the high proportion of patients to whom antifungal therapy was given based on an individualized decision.

The aim of this prospective study was to establish the sensitivity, specificity and negative predictive value of this innovative diagnostic and therapeutic approach based on risk profile and driven by clinical criteria to select patients with persistent febrile neutropenia for antifungal therapy and to compare its efficacy with that of universal empirical antifungal therapy.

Design and Methods

Ethics statement

This study was approved by the Ethics Committee and the Infections Committee (PI0068/2009) of the University Hospital Virgen del Rocío, Sevilla (Spain) and was performed in accordance with the Declaration of Helsinki. Written consent was not required.

Patients and methods

This was a prospective study of consecutive, persistent, febrile neutropenia episodes in patients with hematologic malignancies or HSCT recipients admitted to the Hematology Service of a tertiary care center from October 2007 to October 2009.

Patients were included in the study if they fulfilled the following criteria: (i) age over 14 years; (ii) neutropenia following chemotherapy or HSCT (absolute neutrophil count $<0.5\times10^9$/L or $<1.0\times10^9$/L if rapid decrease was predicted in the following 24-48 h); and (iii) persistent fever (more than 96 h of axillary temperature >38°C recorded twice or >38.3°C recorded once) refractory to empirical antibacterial therapy and without an etiological diagnosis.[7] Patients with a solid neoplasm, neutropenia secondary to other causes and persistent fever with known etiology were not included.

Demographic data, variables related to the hematologic diseases and persistent febrile neutropenia episodes were prospectively recorded.

Definitions

For the final diagnosis of an episode of persistent, febrile neutropenia: (i) infectious fever (other than IFI) was considered proven if there was an organ-specific or systemic infection and microbes were isolated, and probable when microbes were not isolated, but there was response to empirical antimicrobial therapy; (ii) tumor fever was present when active hematologic disease was demonstrated and there was a response to non-steroidal anti-inflammatory drugs (NSAID) or steroids in the absence of proven or probable infection; (iii) drug fever was defined when the fever was temporally related to drug administration and disappeared 24-48 h after withdrawal of the drug, in the absence of proven or probable infection. In all cases it was necessary to rule out a probable or proven IFI. Possible, probable and proven IFI were defined according to EORTC/MSG criteria.[15] Patients considered to be at high-risk of IFI were allogeneic HSCT recipients and patients with acute myeloblastic leukemia receiving induction or re-induction chemotherapy.

The efficacy end-point was an overall successful response of a five-component end-point, used in previous studies of empirical antifungal therapy:[7-9;16;17] successful treatment of any baseline fungal infection, absence of any breakthrough fungal infection during therapy or within 7 days after completion of therapy, survival for 7 days after completion of therapy, no premature discontinuation of antifungal therapy because of drug-related toxicity or lack of efficacy, and resolution of fever (temperature below 38°C for at least 48 h) during neutropenia.

The 30-day crude mortality was defined as death from any cause within the 30 days after the onset of febrile neutropenia. IFI-related mortality was defined as death during treatment of a probable or proven IFI with refractory underlying disease (progression or failure to improve) in the absence of any other condition believed to have caused death.

Severe sepsis and septic shock were defined according to internationally accepted criteria[18] and profound neutropenia was defined as an absolute neutrophil count less than 0.1×10^9/L.[5]

Antimicrobial prophylaxis protocol

Every patient received prophylaxis with levofloxacin (500 mg/day from the first day of chemotherapy or transplant conditioning until the onset of fever) and trimethoprim/sulfamethoxazole 800/160 mg on alternative days. Antifungal prophylaxis was administered only to allogeneic HSCT recipients and patients with chronic graft-*versus*-host disease, with fluconazole 400 mg/day or posaconazole 200 mg tid, respectively.

Management of febrile neutropenia

Routine management of febrile neutropenia episodes included a complete physical examination, a chest X ray, blood cultures (catheter and peripheral blood samples) and additional samples from infected sites as clinically indicated. After obtaining cultures, empirical antimicrobial therapy was started with an antipseudomonal beta-lactam with or without an aminoglycoside. A glycopeptide was added in patients with severe sepsis or septic shock, suspected catheter infection or severe mucositis, according to IDSA recommendations.[5] Blood cultures were repeated within 72 h if initial results were negative.

Those patients with neutropenia and fever after 5 days of empirical antibacterial therapy, without an etiological diagnosis, were defined as patients with persistent febrile neutropenia and were included in the study. The following diagnostic and thera-

peutic approach recommended by the Andalusian Society of Infectious Diseases[12] was applied in order to select patients for antifungal therapy.

Diagnostic and therapeutic approach to episodes of persistent febrile neutropenia

The first step was to evaluate the severity of the episode (severe sepsis or septic shock) and the second step was to identify any clinical infectious foci of possible fungal etiology.

For patients who did not have either severe signs or infectious foci, antifungal therapy was not initially indicated and further diagnostic evaluations were performed, including serial serum GM tests twice a week (with an index >0.5 considered positive), thoracic thin-section computed tomography (TSCT), abdominal ultrasonography, repeated blood cultures and other ancillary tests until an etiological or syndromic diagnosis was reached or the fever disappeared (*Online Supplementary Table S1*).

For the rest of the patients, antifungal therapy was indicated with the most appropriate antifungal agent for the most likely etiology of the IFI[8-9] according to the following clinical criteria: (i) in patients with signs of severe sepsis or septic shock, caspofungin (70 mg/day and 50 mg/day on the following days) was indicated as primary therapy or liposomal amphotericin (3-5 mg/kg/day) as alternative therapy; (ii) in patients without severe sepsis or septic shock and with any infectious foci suspected of being of fungal etiology: pulmonary, central nervous system and sinus, voriconazole (6 mg/kg/day and 4 mg/kg/day on the following days) was used as primary therapy and liposomal amphotericin (3-5 mg/kg/day) or caspofungin (70 mg/day and 50 mg/day on the following days) as an alternative therapy, while in the case of an abdominal or skin focus, caspofungin (70 mg/day and 50 mg/day on the following days) was indicated as primary therapy and liposomal amphotericin (3-5 mg/kg/day) or fluconazole (50-800 mg/day) as an alternative therapy; (iii) in patients with GM detected in the serum (index ≥0.5), voriconazole (6 mg/kg/day and 4 mg/kg/day on the following day) was initiated (*Online Supplementary Table S1*).

The diagnostic work-up established by the study approach entailed serum GM tests performed routinely in all patients twice a week and whenever respiratory symptoms or signs appeared; thoracic TSCT in every patient between the 5th and 7th day of fever and/or if respiratory symptoms or signs developed. Bronchoscopy with bronchoalveolar lavage led by thoracic TSCT was performed when clinically possible in patients with pulmonary infiltrates, for microbiological investigation of bacteria, fungi, *Pneumocystis jirovecii* and mycobacteria stains and cultures, shell vial and viral culture for cytomegalovirus and a rapid test (immunofluorescence) for respiratory viruses (syncytial respiratory virus and influenza virus). In patients with an abdominal focus (painful hepatomegaly and/or elevated serum phosphatase alkaline in which hepatosplenic candidiasis was suspected, or a suspicion of necrotizing enterocolitis without response to supportive management and antibacterial therapy) abdominal ultrasound and/or abdominal computer tomography were performed. Other imaging techniques, invasive procedures such as endoscopy or biopsy and additional cultures of infected sites were performed as clinically indicated (Figure 1).

Statistical analysis

A descriptive analysis was made of the clinical syndrome at presentation, final diagnosis and outcome of every episode of persistent febrile neutropenia, the global incidence of proven and probable IFI and the etiology.

A comparative analysis was performed of the incidence of proven or probable IFI and IFI-related mortality according to whether antifungal therapy was indicated or not. The number of days between fever onset and the start of antifungal therapy in patients with IFI was also analyzed in order to determine whether a delay in antifungal therapy after the 5th-7th day from fever onset (in comparison with the standard IDSA approach) could have affected IFI-related mortality. A sub-analysis of the incidence of proven and probable IFI and IFI-related mortality in IFI high-risk patients was also performed.

The sensitivity, specificity and negative predictive value of the diagnostic and therapeutic approach were analyzed in order to

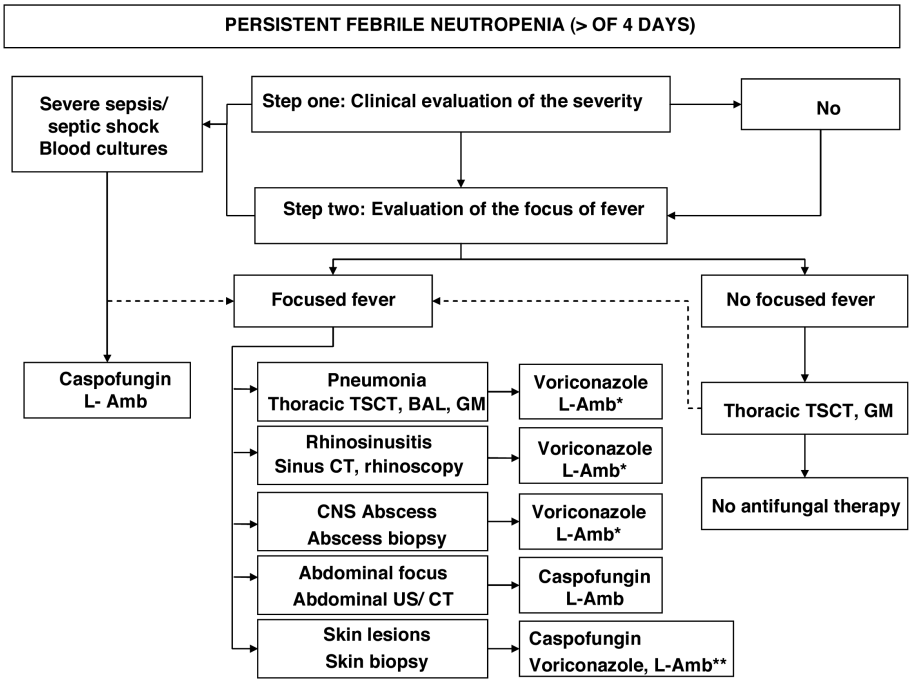

Figure 1. Diagnostic and therapeutic approach in persistent febrile neutropenic patients with hematologic malignancies or hematopoietic stem cell transplant recipients. TSCT: thin-section computed tomography; BAL: bronchoalveolar lavage; GM: serum galactomannan antigen test; CNS: central nervous system; US: ultrasound; L-Amb: liposomal amphotericin; *Liposomal amphotericin is the antifungal therapy of choice if mucormycosis is suspected.; **Voriconazole and/or liposomal amphotericin is the antifungal therapy of choice if *Aspergillus* spp., *Scedosporium* spp. or *Fusarium* spp. is suspected.

assess the usefulness of this strategy in the selection of patients for antifungal therapy. Possible, probable and proven IFI were considered for these calculations. The overall successful response rate was analyzed according to the same criteria of efficacy as those described by Walsh *et al.*[9]

Statistical analyses were performed with software from the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 18.0.

Results

Study population

Eighty-five episodes of persistent febrile neutropenia were recorded in 72 patients during the study period. The median age of the patients was 47 years (range, 15-75), 48.2% were males and 41.7% were considered at high risk of IFI (Table 1).

Antifungal therapy

After initial evaluation, antifungal therapy was indicated between the 5th and 7th days from fever onset in 32 episodes (37.6%), mainly due to pulmonary infiltrates and an abdominal focus of infection. In 20 episodes (23.5%), antifungal therapy was indicated after the 7th day, mostly due to detection of pulmonary infiltrates in TSCT (10.5%). Overall, an indication for antifungal therapy was established in 52 episodes (61.2%) and the median duration of antifungal therapy was 11 days (range, 2-164). The main antifungal drugs used were caspofungin and voriconazole in 24 (28.2%) and 22 (25.9%) episodes, respectively, followed by liposomal amphotericin (n= 4, 7.7%) and fluconazole (n=2, 3.8%). In the remaining episodes of persistent febrile neutropenia (n=33, 38.8%),

Table 1. Basal characteristics of patients and episodes of persistent febrile neutropenia (PFN).

Baseline characteristics	Not IFI high-risk N.	IFI high-risk[1] N.	Total N. (%)
Patients' characteristics	**n=42**	**n=30**	**n=72**
Underlying hematologic disease			
Acute myeloblastic leukemia	3	22	25 (34.7)
Lymphoma	17	1	18 (25)
Multiple myeloma	11	-	11 (15.3)
Acute lymphoblastic leukemia	2	2	4 (5.5)
Myelodysplastic syndrome	2	2	4 (5.5)
Chronic lymphoblastic leukemia	3	-	3 (4.2)
Chronic myeloblastic leukemia	-	1	1 (1.4)
Others	4	2	6 (8.3)
Characteristics of PFN episodes[2]	**n=50**	**n=35**	**n=85**
Median days of fever, (range)	9 (5-33)	12 (5-37)	10 (5-37)
Median days of neutropenia, (range)	10 (5-63)	23 (6-56)	14 (5-63)
Profound neutropenia (ANC[3] <100/μL)	49	35	84 (98.8)
Risk factors for invasive fungal infection			
Acute myelobastic leukemia in induction or reinduction phase	-	20	20 (23.5)
Allogeneic HSCT[4]	-	15	15 (17.6)
Prior IFI[5] episodes	1[6]	0	1 (1.2)

[1]IFI-high-risk patient: allogeneic HSCT recipient or patient with acute myeloblastic leukemia receiving induction or re-induction chemotherapy; [2]PFN episodes. persistent febrile neutropenia episodes; [3]ANC: absolute neutrophil count; [4]HSCT: hematopoietic stem cell transplantation; [5]IFI: invasive fungal infection; [6]Hepatosplenic candidiasis during induction chemotherapy in one patient with acute myeloblastic leukemia in consolidation phase at the time of the study.

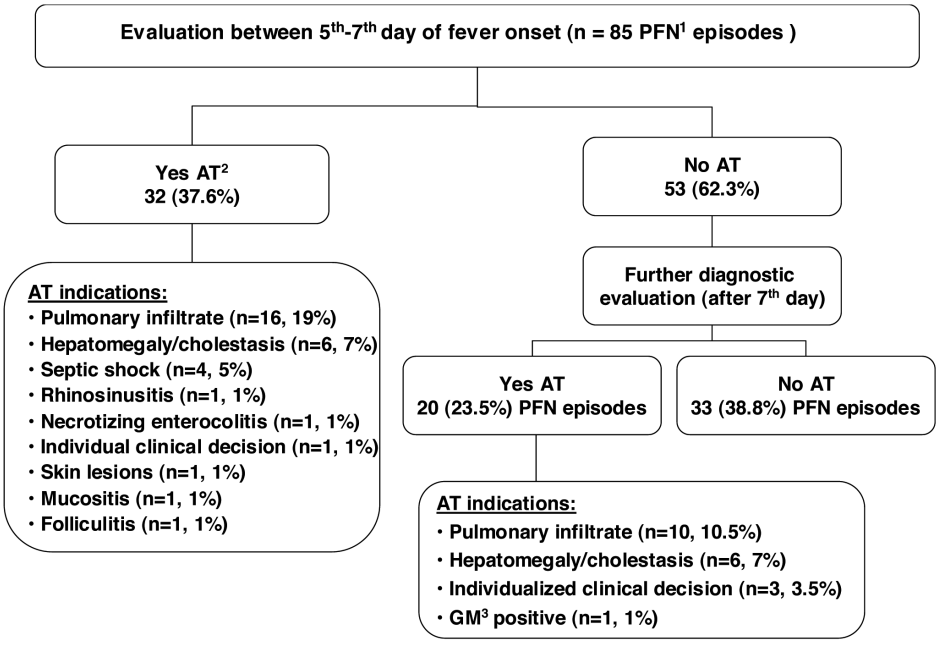

Figure 2. Results of the implementation of the diagnostic and therapeutic approach in persistent febrile neutropenic patients with hematologic malignancies or hematopoietic stem cell transplant recipients. [1]PFN: persistent febrile neutropenia; [2]AT: antifungal therapy; [3]GM: serum galactomannan antigen test.

and following the diagnostic and therapeutic approach steps, antifungal therapy was not indicated (Figure 2).

Thirty-five episodes of persistent febrile neutropenia (41.2%) occurred in patients considered at high-risk for IFI and antifungal therapy was indicated in 26 of these cases (74.3%).

The mean duration of fever was longer in episodes for which antifungal therapy was given than in episodes in which antifungal therapy was not given (13.9±7.2 *versus* 9.91±4.9 days; *P*=0.006) whereas there were no differences in the mean duration of neutropenia between episodes in which antifungal therapy was or was not used (19.8±11.2 *versus* 15.8±11.8 days; *P*=0.123).

The most frequent final diagnosis of episodes of persistent febrile neutropenia was non-fungal infection (n=46, 54.1%), mostly presenting as non-focused fever or pneumonia without isolation of microbes but with a favorable response to antibacterial therapy (Table 2).

Proven and probable invasive fungal infections

The overall incidence of proven or probable IFI was 14.1% (12 IFI episodes out of 85 episodes of persistent febrile neutropenia) with 11 cases diagnosed as baseline IFI and one as breakthrough IFI. There were ten episodes of possible IFI. All IFI episodes appeared in the group of patients who received antifungal therapy. The incidence of proven or probable IFI was 20% (7/35) in high-risk patients and 10% (5/50) in the remaining (*P*=0.219). The main etiology of these IFI episodes was molds (n=8, 66.7%). None of the IFI was a relapse of a previous episode.

The mean number of days between the onset of fever and the start of antifungal therapy was similar in patients who developed IFI (6.8±2 days) and in those who did not (7±3.8 days) (*P*=0.85). Every patient who developed IFI and died during the follow up had received antifungal therapy between the 5th and 7th day after the onset of fever (Table 3).

The sensitivity, specificity and negative predictive value of the diagnostic and therapeutic approach for selecting patients who did not need antifungal therapy were 100% (CI 95% 85.1-100), 54.2% (CI 95% 40.3-64.2) and 100% (CI 95% 89.6-100), respectively (Table 4).

Outcome and patients' survival

According to the five-component end-point criteria, the overall successful response to treatment in patients with persistent febrile neutropenia episodes was 36.5% after the application of the diagnostic and therapeutic approach and 33.9% and 33.7% when empirical antifungal therapy was administered in the controlled trial by Walsh *et al.*[9] (Table 5).

The 30-day crude mortality rate was 15.3% (11/72 patients) overall, 21.7% (10 out of 46) in the group of patients who received antifungal therapy and 3.8% (1 out of 26) in the group of patients who did not.

The IFI-related mortality rate was 2.8% (2/72): both of the two patients who died of IFI-related causes received antifungal therapy. One patient died of probable invasive pulmonary aspergillosis after re-induction chemotherapy for relapsed myeloblastic leukemia and the other died of proven invasive candidiasis (*Candida albicans*) after a second (of a tandem) autologous HSCT for relapsed seminoma.

Within the group of patients at high risk of IFI, the 30-day crude mortality was 10% (3 out of 30 patients) and IFI-related mortality was 3% (1 out of 30 patients). There was no difference in mortality between patients at high risk of IFI and those not at high risk (*P*=0.754).

Table 2. Final diagnosis of persistent febrile neutropenia (PFN) episodes classified according to the indication or not for antifungal therapy.

Final diagnosis of PFN episodes	Antifungal therapy N. (%)	No antifungal therapy N. (%)
Infection	**43 (82.7)**	**25 (75.7)**
Invasive fungal infection	22 (42.3)	0
Proven IFI[1]	3 (5.8)	0
Probable IFI	9 (17.3)	0
Possible IFI	10 (19.2)	0
Non-fungal infection	21 (40.4)	25 (75.7)
Not infection	**9 (17.3)**	**7 (21.2)**
Tumor fever	5 (9.6)	5 (15.1)
Drug fever	2 (3.8)	2 (6.1)
Pulmonary thromboembolism	1 (1.9)	0
GVHD[2]	1 (1.9)	0
Unknown fever	**0**	**1[3] (3)**
TOTAL	**52 (100)**	**33 (100)**
IFI high-risk episodes[4]	**26 (50)**	**9 (27.3)**
Non IFI high-risk episodes	**26 (50)**	**24 (72.7)**

*[1]IFI: invasive fungal infection; [2]GVHD: graft-*versus*-host disease; [3]This patient had a lymphoma and during neutropenia post chemotherapy presented with non-focused fever, without signs of severity, and negative radiological and microbiological tests, which resolved without antifungal therapy; [4]IFI high-risk episodes: persistent febrile neutropenia episodes in allogeneic hematopoietic stem cell transplant recipients and in patients with acute myeloblastic leukemia receiving induction or re-induction chemotherapy.*

Discussion

The results of this study demonstrate that a diagnostic and therapeutic approach based on risk profile and driven by clinical criteria has a high sensitivity and negative predictive value for selecting patients who do not need antifungal therapy, who accounted for nearly 40% of the episodes of persistent febrile neutropenia in our series.

These results corroborate the findings of our previous pilot study[10] in which this diagnostic and therapeutic approach[12] was applied in a cohort of 66 consecutive episodes of persistent febrile neutropenia. The main conclusion of that study was that the approach was safe and effective without increasing the incidence of IFI or IFI-related mortality while avoiding over-treatment caused by universal empirical antifungal therapy.[5;7-9;17;19] However, those results were influenced by the lack of the serum GM test, which could have led to an underestimate of the incidence of probable aspergillosis, and by the high proportion (34.6%) of use of antifungal therapy following individualized clinical decisions based on risk profile rather than on clinical criteria and diagnostic tests. The current study overcomes those limitations, incorporating improvements to the approach and its implementation, and confirms the effectiveness and safety of the investigated strategy.

Recently some authors have proposed other approaches for selecting patients guided by clinical criteria and risk profiles.[11-14;20;21] Maertens *et al.*[14] designed a pre-emptive approach to antifungal therapy based on serial serum GM tests in IFI high-risk hematology patients receiving anti-

Table 3. Description of proven and probable invasive fungal infections, the positive diagnostic test that established their etiology and clinical outcomes.

Diagnosis and etiology	Clinical syndrome	Radiological test	Microbiological test	Days fever onset- AT[1]	Type of IFI	Antifungal therapy	Outcome
Proven *Aspergillus fumigatus*	Pulmonary	Thoracic TSCT[2]	BAL[3], LB[4]	+7	Baseline	Voriconazole [#]	Cure
Probable *Aspergillus spp.*	Pulmonary	Thoracic TSCT	BAL	+5	Baseline	Voriconazole [#]	Cure
Probable *Aspergillus spp.*	Individualized clinical decision	Thoracic TSCT	GM[5]	+8	Break-through	Amphotericin [#] Voriconazole [Ψ]	Cure
Probable *Aspergillus spp.*	Pulmonary	Thoracic TSCT	GM	+6	Baseline	Voriconazole [#]	Cure
Probable *Aspergillus spp.*	Pulmonary and abdominal	Thoracic TSCT	GM	+7	Baseline	Voriconazole [Ψ]	IFI[6]-related death
Probable *Aspergillus spp.*	Pulmonary	Thoracic TSCT	GM	+10	Baseline	Voriconazole [#]	Cure
Probable *Aspergillus spp.*	Pulmonary	Thoracic TSCT	GM	+5	Baseline	Voriconazole [#]	Cure
Probable *Aspergillus spp.*	Pulmonary	Thoracic TSCT	GM	+11	Baseline	Voriconazole [#]	Cure
Probable hepatosplenic candidiasis	Abdominal, ESAF[7]	Abdominal US[8]	-	+5	Baseline	Caspofungin [#]	Death not related to IFI
Proven *Candida albicans*	Severe sepsis/ septic shock	Thoracic TSCT, Abdominal US	BC[9]	+6	Baseline	Caspofungin [#] Voriconazole [Ω]	IFI-related death
Proven *Candida tropicalis*	Abdominal	-	BC	+5	Baseline	Caspofungin [#] Fluconazole [Ψ]	Death not related to IFI
Probable hepatosplenic candidiasis	Abdominal, ESAF	Abdominal CT[10]	-	+7	Baseline	Caspofungin [#]	Cure

[1]AT: antifungal therapy; [2]Thoracic TSCT: thoracic thin section computed tomography; [3]BAL: bronchoalveolar lavage; [4]LB: lung biopsy; [5]GM: serum galactomannan antigen test; [6]IFI: invasive fungal infection; [7]Abdominal US: abdominal ultrasound; [8]ESAF: elevated serum alkaline phosphatase level (supporting microbiological criteria are not required for probable category); [9]BC: blood cultures; [10]Abdominal CT: abdominal computed tomography. [#]Primary antifungal therapy; [Ω]Addition of antifungal agent to primary therapy; [Ψ]Change of antifungal drug.

fungal prophylaxis against *Candida* spp. In a small subgroup of patients with persistent febrile neutropenia (30 out of 136 patients, 22%) the use of antifungal therapy was reduced from 35% to 7.7% without an increase in IFI incidence or IFI-related mortality. However, the number of patients was relatively small and the study did not include recipients of non-myeloablative allogeneic or autologous HSCT, since this approach is complicated to use in daily clinical practice. More recently Cordonnier *et al.*[13] published the results of a randomized multicenter study comparing universal empirical antifungal therapy with pre-emptive therapy (150 patients with hematologic malignancies in each arm). Antifungal therapy was administered to 59.8% of the patients in the conventionally treated group and to only 1.8% in the pre-emptively treated group, with similar overall mortality in the two groups. The results of this study, which also excluded allogeneic HSCT recipients, suggest that pre-emptive antifungal therapy is not inferior to universal empirical antifungal therapy; the authors concluded that further studies are needed to investigate the safety and usefulness of this new approach.[13]

With the present study, we have established the usefulness of a tailored diagnostic and therapeutic approach[12] based on clinical criteria and patients' risk profile in a fairly large series of patients with hematologic malignancies. The main strength of our approach is its safety, based on the high negative predictive value of the approach. Furthermore, it was applicable and equally safe in patients at very high risk of developing IFI, including allogeneic HSCT recipients and patients with relapsed leukemia who represented 41.6% of the study population, and patients with prolonged neutropenia (median of 14 days) or profound neutropenia, who accounted for 98.8% of the study population.

Table 4. Sensitivity and specificity of the diagnostic and therapeutic approach for selecting hematology patients with persistent febrile neutropenia for antifungal therapy.

	Invasive fungal infection N.	Not invasive fungal infection N.	Total N.
Antifungal therapy	22[1]	30	52
No antifungal therapy	0	33	33
Total	22	63	85

	Value	95% C. I. Lower limit	95% C. I. Upper limit
Sensitivity	100%	85.1	100
Specificity	52.4 %	40.3	64.2
Positive predictive value	42.3%	29.9	55.8
Negative predictive value	100%	89.6	100

[1]22: three proven, nine probable and ten possible invasive fungal infections were considered.

The overall success rate of the approach, determined on the basis of a five-component end-point, was similar to that found by Walsh *et al.*[9] in a controlled trial of universal empirical antifungal therapy, but with the main difference that in our study antifungal therapy was indicated in only 60% of the episodes of neutropenia.

Unlike other series,[13-14;20] in this study the choice of antifungal drug was guided by the most probable fungal etiology in each case depending on clinical criteria (e.g. septic shock) and/or the results of the diagnostic work-up (e.g. halo sign) following international guidelines for antifungal therapy.[19;22] The advantage of this personalized choice of

Table 5. Comparison of the overall success rate obtained by the diagnostic and therapeutic approach and in the clinical trial reported by Walsh *et al.*[9] in which universal empirical antifungal therapy was used.

End point	Diagnostic and therapeutic approach (Cisneros *et al.*[12]) (N. = 85)	Caspofungin (Walsh *et al.*[9]) (N. = 556)	Liposomal amphotericin B (Walsh *et al.*[9]) (N.=539)
Overall successful response, N. (%)	31 (36.5)	190 (33.9)	181 (33.7)
Components of the primary end-point			
Successful treatment of baseline proven or probable IFI[1]	9/11 (81.8)	14/27 (51.9)	7/27 (25.9)
Absence of proven or probable breakthrough IFI	84/85 (98.8)	527 (94.8)	515 (95.5)
Survival for ≥ 7 days after completion of study therapy	74/85 (87)	515 (92.6)	481 (89.2)
Resolution of fever for at least 48 h during neutropenia	36/85 (42.3)	229 (41.2)	223 (41.4)
No therapy discontinuation prematurely because of toxicity or lack of efficacy	80/85 (94.1)	449 (89.7)	461 (85.5)

Proven and probable [1]IFI: invasive fungal infections were considered.

antifungal therapy is that the patients received the most appropriate antifungal drug early in the clinical course of their disease. This fact could explain the high IFI cure rate obtained in our study: 66.7% (8/12). Although voriconazole is not approved for use in persistent febrile neutropenia,[5] it is the drug of choice for invasive aspergillosis[19;23] and should be used from the beginning if *Aspergillus* spp. is the most probable etiology of an infection. In recent studies[24-25] high rates of breakthrough invasive aspergillosis have been found among patients receiving caspofungin for persistent fever. In a study by Lafaurie *et al.*[25] the suspicion of invasive aspergillosis led to the interruption of caspofungin empirical therapy and a switch to voriconazole in all but one case. These supposed breakthrough infections appeared at a median of only 8 days after the initiation of empirical antifungal therapy, but the authors recognized that, at least in some of these patients, invasive aspergillosis was probably present from the onset of the fever, but that it was overlooked because computed tomography of the chest was not included in the protocol at the start of empirical antifungal therapy and was not, therefore, always performed.

On the other hand, our study showed that the most frequent cause of persistent fever was a non-fungal infection that responded well to antibacterial therapy, whereas probable or proven IFI accounted for only 14.1% of the episodes. In addition, the incidence of proven or probable IFI in this study, which included a large proportion of patients at very high risk of IFI, was similar to that in other series,[11,14,25] as was the IFI-related mortality rate of 2.7%.[10,21,25]

Our study has some weaknesses. First of all, it was a non-randomized, interventional study. Nevertheless, this study included every persistent febrile neutropenia episode occurring over a 2-year period in a tertiary hospital with an active HSCT program. Also, the specificity of this approach in the selection of persistent febrile neutropenia episodes of fungal etiology was low because, although some unnecessary antifungal therapy was avoided, 76.9% of patients who received antifungal therapy did not have either proven or probable fungal infection. However, there was still a global reduction of antifungal therapy of 38.8% compared to that administered using the standard approach.[5] The development of new diagnostic tests such as β-D-glucan and specific fungal polymerase chain reaction anaysis[26-29] would improve the specificity of this approach in the future. Finally, our proposed approach requires intensive clinician involvement and diagnostic work-up together with prompt availability of the results of critical diagnostic tests (computed tomography scan, bronchoalveolar lavage and GM).

In conclusion, based on the high negative predictive value of this diagnostic and therapeutic approach in patients with hematologic malignancies or HSCT recipients with persistent febrile neutropenia, the approach is useful for identifying patients who are not likely to develop invasive fungal infection and do not, therefore, require antifungal therapy, and has an effectiveness similar to that reported in controlled trials in which empirical antifungal therapy was used universally.

Authorship and Disclosures

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