

The Management of Invasive Fungal Infections: What to Consider in Empirical Treatment?

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ABSTRACT

Invasive fungal infections (IFI) are a major cause of morbidity and mortality in immunocompromised patients. *Candida* and *Aspergillus* are the most common fungi that lead to IFI. While invasive *Candida* infections are most commonly seen in patients in intensive care units (ICUs) and very low birth weight infants, aspergillosis is most frequent in immunocompromised patients, especially in patients with hematological malignancies and in those undergoing hematopoietic stem cell transplantation (HSCT). Empirical treatment should be considered in all high-risk patients with hematological malignancies suspected of having IFIs.

Keywords: Invasive fungal infection, Empirical antifungal therapy

ÖZET

İnvaziv Fungal Enfeksiyonların Yönetimi: Ampirik Tedavide Dikkate Alınması Gerekenler

İnvaziv fungal enfeksiyonlar (İFİ) immüno-kompromize hastalarda morbidite ve mortalitenin önemli bir nedenidir. *Candida* ve *Aspergillus*, İFİ'ye en sık yol açan mantarlardır. İnvaziv *Candida* enfeksiyonları en sık yoğun bakım ünitesi (YBÜ) hastalarında ve çok düşük doğum ağırlıklı bebeklerde görülmekte iken, aspergilloz özellikle hematolojik malignansili hastalarda ve hematopoietik kök hücre nakli (HKHN) yapılanlarda olmak üzere en sık immüno-kompromize hastalarda görülmektedir. Ampirik tedavi İFİ olduğu şüphelenilen hematolojik malignansili tüm yüksek riskli hastalarda düşünülmelidir.

Anahtar Kelimeler: İnvaziv fungal enfeksiyon, Empirik antifungal terapi

Epidemiological Facts in Invasive Fungal Infections - What Has Changed?

The prevalence of IFIs is not known, but population-based survey data indicate a prevalence of 12-17 per 100,000 population.¹ The annual number of deaths in which an IFI was written on the death certificate increased from 1,557 to 6,534—a 320% increase from 1980 through 1997 in the United States.² Along with the increase in the number of IFIs, there is an alteration in the type of fungal infections. In a retrospective review of autopsy cases in Toho University, Japan, a total of 411 cases of IFIs were detected among 10,297 autopsies. The prevalence of candidiasis decreased from 3.6% (1981-93) to 2.0% (1994-2006), while that of aspergillosis increased throughout the 52-year period and reached 2.0%.³ Additionally, similar to the development of antibiotic resistance, the use of broad-spectrum antifungal agents such as voriconazole has led to the emergence of IFI caused by the mucormycetes class of fungi.⁴ In a case-control study involving 14 leukemic and 13 HSCT patients, voriconazole prophylaxis was identified as an independent risk factor, increasing the risk for invasive mucormycosis by more than 10-fold.² Singh et al.⁵ performed a prospective, matched case-control study of 50 solid-organ transplant recipients and found that voriconazole and/or caspofungin use increased the risk of mucormycosis by 4.4 times.

In another single-center series of autopsy-proven patients with hematologic malignancies, the prevalence of invasive aspergillosis and mucormycosis rose from 16% to 19% and from 1% to 3% respectively, while the prevalence of invasive candidiasis fell from 13% to 8%.from 1989 through to 2003.⁶ The shift toward more invasive mold infections is critical as the overall 1-year survival is lower in invasive aspergillosis compared to invasive candidiasis in both HSCT (25.4% vs. 33.6%) and solid-organ transplant patients (59% vs. 66%).^{7,8}

Another trend observed is the increasing incidence of non-albicans *Candida* spp. *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata* have been isolated much more frequently as causes of invasive candidiasis worldwide, although *C. albicans* remains the most common.⁹

Diagnostics

Despite advances in serological, molecular and imaging modalities, early diagnosis of IFI remains problematic. This situation becomes more critical as IFIs are most commonly seen in immunocompromised patients.

Although traditional culture-based tests produce low outputs and long time delays, they are inexpensive and provide valuable material on which to perform drug-sensitivity testing, which has become increasingly important, due to changing patterns of resistance. Histological evaluation of tissue specimens for fungi can be done rapidly, however, tissue biopsy may be too invasive for most immunosuppressed patients and simple light microscopy may not be specific enough for identification of some fungal species.

Galactomannan, an important component of the cell wall of *Aspergillus* spp., is released during early stages of growth, allowing the tests for its presence to be fairly sensitive (71%) and specific (89%).¹⁰ It can be detected in serum and in bronchoalveolar lavage (BAL) fluid thus providing a surrogate marker for the diagnosis of invasive aspergillosis. Although the commercially available enzyme-linked immunosorbent assay (ELISA) kits demonstrate good specificity, they have a variable sensitivity ranging from 17% to 100%, mainly depending on the cut-off value used to determine the positivity.¹¹ Until recently, the manufacturers recommended a serum ratio of 1.5. However, recent studies have used a cut-off ratio of 0.5–1.0, and the US Food and Drug Administration (FDA) approved a value of 0.5. This cut-off ratio greatly increases the sensitivity at some loss of specificity. Galactomannan (GM) is also not specific for aspergillosis and can cross react with other fungal species such as *Fusarium*. A positive or negative GM test, whilst useful for determining a diagnosis of aspergillosis, does not exclude a diagnosis of mucormycosis.

There are some considerations in using galactomannan testing in medium high-risk patients with hematological malignancies (Table 1). Causes for false-positivity, cross reactivity and low sensitivity in galactomannan test are of concern and are presented in Table 2.¹² The most common reason reported for false-positive GM results is the concomitant

Table 1. Use of galactomannan testing for monitoring in medium high-risk patients
<p>Frequency</p> <p>Two or three times weekly during high level immunosuppression</p> <p>Criteria for positivity</p> <p>Two consecutive serum specimens with GMI > 0.5, and the test should be repeated before beginning therapy for invasive aspergillosis</p> <p>Considerations</p> <ul style="list-style-type: none"> Galactomannan contamination may cause false positivity Cross-reactivity caused by similar cell wall galactomannan may cause false positivity Numerous foods (pasta, rice, etc.) that contain galactomannan may cause false-positivity Damage to the gut wall by cytotoxic therapy, irradiation, or graft-versus-host disease may cause false-positivity Mold-active antifungal drugs may cause false-negativity: repeat the test before implementing therapy for invasive aspergillosis False-positive or false-negative results may occur for other reasons: clinical correlation is mandatory
<p>GMI: galactomannan index</p>

use of piperacillin-tazobactam. The use of antimold prophylaxis is known to attenuate the value of the GM assay. There is also some cross-reactivity with penicillium and other endemic fungi, such as histoplasma and blastomyces. Factors including diet, ice-pops, infections or concomitant drugs may affect GM test results.

Recently it has been indicated that galactomannan testing is not influenced by prophylactic treatment because of lower quantity of galactomannan.¹³

The recent development of molecular amplification methods, such as polymerase chain reaction (PCR) and nucleic acid sequence based amplification (NASBA) for the rapid diagnosis of infections holds promise for increasing the sensitivity and specificity further, but standardization issues of the assays remain unresolved. PCR testing is not included within the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Antigen detection and PCR have also been performed on other specimens such as BAL fluid. Although more prone to contamination, the negative predictive value of the assay remains high and these specimens may have some diagnostic utility.

Other surrogate markers for invasive fungal infection include the detection of secondary metabolites, proteomic approaches and the use of novel immunolabelling approaches to positron emission tomography.¹⁴

Testing of beta-D-glucan (a major cell wall constituent characteristic of most fungi), although approved by some reports for detecting invasive candidiasis and other fungal infections (except mucormycosis), has not received widespread acceptance due to difficulties in performance techniques and lack of specificity.¹⁵

Computed tomography (CT) scans of the chest are widely used as diagnostic tools when dealing with pulmonary or hepatic IFI in immunocompromised patients. Fungal infections such as invasive aspergillosis present with nodules surrounded by haziness (halo sign) and may be associated with cavitary lesions. Identifying these lesions early allows earlier initiation of appropriate antifungal therapy. Similarly, defects in the liver architecture noted on CT scanning of the abdomen provide an early sign of an invasive fungal infection involving the liver. Treatment with antifungal drugs based on these early CT findings has been associated with improved survival. Mortality from aspergillosis is >70% if diagnosis is delayed.¹⁶ On the other hand, halo (Aspergillus) or reverse halo sign (mucormycosis)

Table 2. Causes for false-positivity, cross reactivity and low sensitivity in galactomannan test¹³

False-positivity caused by galactomannan contamination	Cross-reactivity caused by similar cell wall galactomannan	Low sensitivity
Piperacillin-tazobactam*	Penicillium spp. including P. marneffeii	Infections caused by Aspergillus fumigatus,****
Amoxicillin-clavulanate**	Histoplasma capsulatum	Patients receiving prophylactic antifungal drugs
Plasmalyte (sodium gluconate)	Geotrichum spp.	Non-severely neutropenic patients (>100 polymorphonuclear leukocytes (PMN)/mm ³)
Other beta-lactam antibiotics (cefepime***, and cefoperazone-sulbactam****)	Neosartoria spp.	During the days prior to the onset of fever and on the first day of fever
Other intravenous hydration or nutrition fluids containing sodium gluconate	Possibly Paecilomyces spp, Alternaria spp.	
Possibly cotton, cardboard, soybean protein	Trychophyton spp, Botrytis spp, Wallemia spp, Cladosporium spp, Bifidobacterium spp	

* 58.3% for serum, 50% for BAL; ** 26.7% for serum, 27.3% for BAL; *** 14.3% for serum, 16.7% for BAL; **** 66.7% for serum, 45.5% for BAL.

on chest CT are not pathognomonic and may be seen in a many infectious (bacterial, mycobacterial, viral or parasitic) and non-infectious (neoplasms, vasculitis, amyloidosis, etc.) diseases.

EORTC/MSG included antigen testing and radiology in the consensus definitions for diagnosing fungal infections.¹⁷

Who is at Risk for Invasive Fungal Infections?

The summary risk of an IFI depends on the overall net state of immunosuppression, especially, the intensity and duration of neutropenia and the epidemiologic exposures encountered. Patients can be classified into three main risk groups according to the degree of immunosuppression:¹⁸

a. High-risk: Patients with profound (absolute neutrophil count <100/mm³) and prolonged (>14 days) neutropenia or an important cell immunity deficiency resulting from chemotherapy, radiotherapy, cytomegalovirus (CMV) infection, graft-versus-host disease (GVHD) or treatment with corti-

steroids, anti-tumor necrosis factor (TNF)-agents or alemtuzumab. Patients with allogeneic stem cell transplantation (SCT) with umbilical cord blood or allogeneic human leukocyte antigen (HLA)-mismatched SCT, allogeneic SCT with GVHD, and acute leukemias (myeloid or lymphocytic) and myelodysplastic syndromes during induction, re-induction or rescue therapy, are included in this group.

b. Medium-risk: Patients with neutropenia duration of 7- 14 days; HLA-matching allogeneic SCT and acute leukemias and myelodysplastic syndromes during consolidation or intensification chemotherapy are included in this group.

c. Low-risk: is characterized by neutropenia of <7 days as occurs frequently in autologous SCT.

The inclusion of a patient in one of the above-mentioned risk groups also depends on the other risk factors shown in Table 3. The assessment of each of these aspects can make us change the initial risk group defined according to criteria of Figure 1.¹⁸

Table 3. Other risk factors of invasive fungal infections			
Personal factors	Comorbid conditions	Immunosuppressive treatment	Environmental factors
Age >65 years	Non-controlled hyperglycemia	Prolonged corticosteroid treatment hyperglycemia	Building works in the local environment
Advanced disease	Cytomegalovirus infection	Alemtuzumab	Rooms without HEPA filters
Previous invasive fungal infection	Infection caused by a respiratory virus	Cytarabine at high doses	Seasonal incidence
Iron overload	COPD	Anti-TNF agents (infliximab)	Weather variation (temperature rainfall humidity wind speed)
Metabolic acidosis	Renal failure	High doses of total body irradiation	Personal habits (smoking, living in countryside, fungus exposure, type of work (e.g. farmer, agriculture)
Malnutrition	Liver failure		Exposure outside (pets, dusty household, construction work)
Transplantation, especially bone marrow transplantation (TLR4-2)	Genetic polymorphisms	MBL, Toll-like receptors	Exposure inside (potted plants, absence of HEPA-filtered rooms, water)
	AIDS		

HEPA: High efficiency particulate air; TNF: Tumor necrosis factor; COPD: Chronic obstructive pulmonary disease; MBL: Mannan binding lectin; AIDS: acquired immune deficiency syndrome

Antifungal Treatment Strategies

Antifungal drug usage can be divided into four strategies for prevention and treatment. These represent a continuum from prophylaxis (administration of drug to high-risk groups without evidence of disease), through empirical (administration of antifungals to neutropenic patients with persistent refractory fever) and pre-emptive, recently called the clinically driven diagnostic approach (using clinical, radiological and laboratory markers to determine the likelihood of disease), to treatment of established fungal infection. The differences between these strategies relate to 'time of commencing antifungal therapy and certainty of the diagnosis of IFI. The main aim of this paper was to discuss empirical treatment.

Empirical Treatment: Pros and Cons

Empirical treatment is defined as systemic antifungal treatment for a single oral temperature measurement of $\geq 38.3^{\circ}\text{C}$ or a temperature of $\geq 38.0^{\circ}\text{C}$ sustained over a 1-h period despite broad-spectrum antibiotics (usually for 4–7 days) in the setting of neutropenia ($<0.5 \times 10^9/\text{L}$) in conditions where clinical, radiological and microbiological diagnostic evaluation has excluded other etiologies but has also failed to document a proven or probable IFI.¹⁹

Empirical treatment is given to medium- high-risk patients with fever that is unresponsive to 48-72 h of broad-spectrum antibiotic therapy, prior to diagnosis. As early diagnosis of IFIs is still challenging, early treatment remains an issue that needs to be addressed in many circumstances. Studies showed that early initiation of therapy seems to improve the

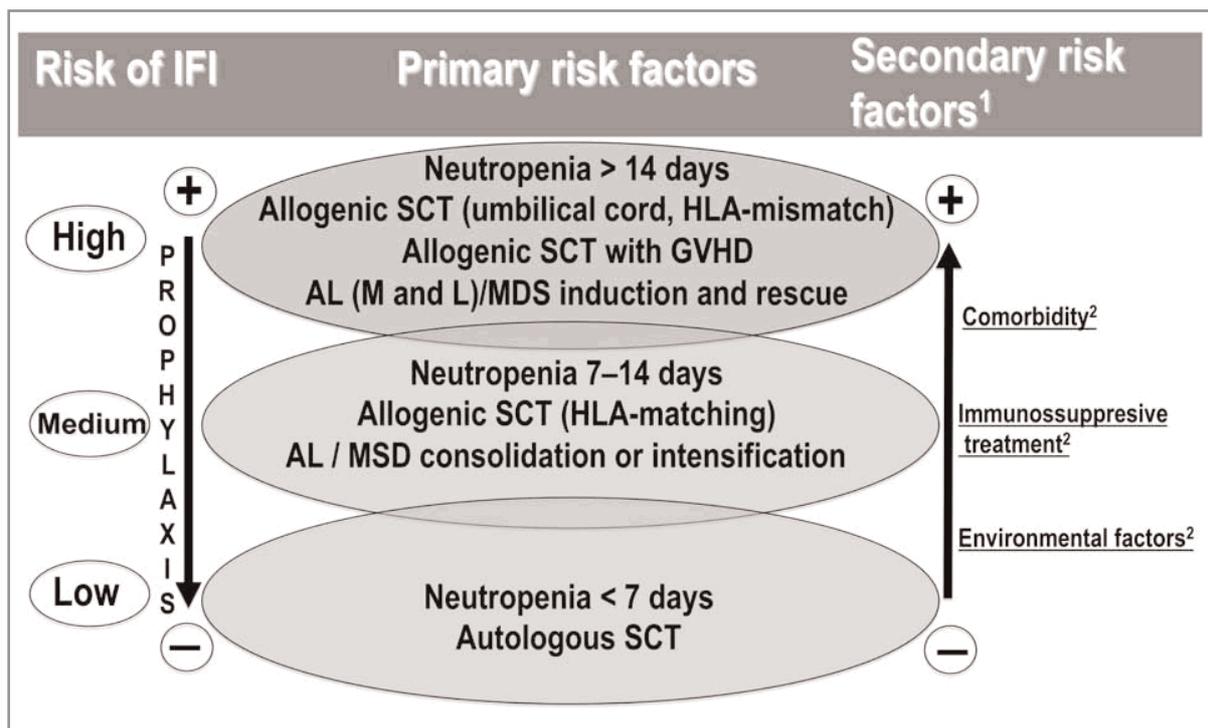


Figure 1. Risk factors of invasive fungal infections

¹ The presence of one or more of these factors may determine an increase of the risk group;

² See Table 3.

IFI: Invasive fungal infections; SCT: stem cell transplantation; HLA: human leukocyte antigen; AL: acute leukemia; GVHD: graft-versus-host disease; M: myeloid; L: lymphocytic; MDS: myelodysplastic syndromes.

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survival rate. Morrell et al.²⁰ showed that administration of antifungal therapy after 12 h of having the first positive blood sample for culture drawn as an independent predictor of hospital mortality.

While making maximum use of available diagnostic tools, and trying to incorporate them into our clinical practice as standardized and valid tools, high-risk patients with hematological malignancies should be given empirical treatment.

The concept of empirical treatment in IFI emerged in 1980's with two studies conducted by the EORTC International Antimicrobial Therapy Cooperative Group²¹ and Pizzo et al.²² These two studies, which used amphotericin B deoxycholate (conventional amphotericin B) in treating IFIs, reported a decrease in the incidence and mortality of IFIs by this approach. However, dose limiting adverse effects of this compound led to studies with

new compounds. Walsh et al.,²³ in their study in 1999, compared liposomal amphotericin B with conventional amphotericin B in the empirical treatment of IFIs. The authors demonstrated that liposomal amphotericin B had similar efficacy to conventional amphotericin B, but with fewer breakthrough fungal infections and a lower frequency of side effects, including infusion-related toxicity, and nephrotoxicity. The greater efficacy of liposomal amphotericin B was attributed to the fact that it was given at a dose of 3 mg or more per kilogram with minimal dose-dependent toxicity.

Thereafter, in 2002 in a study comparing the efficacy of liposomal amphotericin B with a triazole, voriconazole, in the empirical treatment of IFIs, voriconazole did not meet the noninferiority criteria in treating IFIs in an empirical setting compared to liposomal amphotericin B.²⁴ However, the authors stated that the overall response rate among patients

who received voriconazole was similar to the rate among those who received liposomal amphotericin B, and voriconazole was superior to liposomal amphotericin B in reducing breakthrough fungal infections, infusion-related toxicity, and nephrotoxicity. The FDA challenged the authors' conclusions in print and voriconazole is not approved for empiric therapy.²⁵

Another study by Walsh et al.²⁶ investigated the efficacy and safety of caspofungin, an echinocandin, as compared to liposomal amphotericin B. The study was conducted in 1095 patients, 556 receiving caspofungin and 539 receiving liposomal amphotericin B. According to the results of the study, caspofungin was as effective as liposomal amphotericin B in the empirical treatment of IFIs. However, efficacy results of the study by Walsh et al.²⁶ conducted in 2004 should be carefully evaluated. The patient group enrolled in the study was notably a lower risk patient population than the prior empirical studies with Allo-HSCT; the rate being 6.5% for the caspofungin group and 7.2% for the liposomal amphotericin B group. Whereas in the studies by Walsh et al. in 1999 (conventional amphotericin B vs. liposomal amphotericin B)²³ and in 2002 (voriconazole vs. liposomal amphotericin B),²⁴ the allo-HSCT rates were 18.7% and 18.3%, respectively. Also the rate of successful treatment of baseline fungal infection in patients using liposomal amphotericin B in the study by Walsh et al.²⁶ conducted in 2004 was surprisingly lower (25.9%) when compared to the prior empiric studies (66.7% and 81%). This may be due to the fact that in the study by Walsh et al.²⁶ conducted in 2004, the baseline fungal infections caused by rare molds other than *Aspergillus flavus* was higher in the liposomal amphotericin B group compared with the caspofungin group (In caspofungin group isolates included: *Aspergillus candidus* [two], *A. flavus* [two], *A. fumigatus* [five], and *Aspergillus* species not further identified [four]). The liposomal amphotericin B group isolates included *A. flavus* [five], *A. fumigatus* [one], *A. niger* [one], *A. terreus* [one], and *Aspergillus* species not further identified [five]). On the other hand, the preference to include successful treatment of any baseline fungal infection as one of the components of the primary endpoint may be also questionable since in the empiric setting the diagnosis of IFI is not confirmed.

Despite the fact that caspofungin is not recommended in the first-line treatment of invasive aspergillosis and rare molds, the rate of breakthrough infections have been found to be similar between caspofungin and liposomal amphotericin B in this study (5.2% vs. 4.5%). Furthermore nephrotoxicity (2.6% vs. 11.5%), an infusion-related event (35.1% vs. 51.6%), any drug-related adverse event (54.4% vs. 69.3%) or discontinuation of study therapy due to a drug-related adverse event (5% vs. 8%) was significantly lower in the caspofungin group vs. liposomal amphotericin B group.

In pursuit of trying to find a way to prevent drug-related toxicity and costs related to over-treatment, the so-called preemptive treatment approach emerged with a study performed by Maertens et al.²⁷ in 2005. Maertens used galactomannan screening, HRCT and bronchoscopy to diagnose IFIs in high-risk neutropenic patients who had received fluconazole prophylaxis. Among the 41 febrile neutropenia episodes, 9 of them were treated preemptively; in addition, 10 episodes that were not suspected of IFI were treated by antifungal therapy. However, although diagnostic tests were used early in the treatment course, the study failed to identify 3 cases of IFI caused by non-*Aspergillus* species. The 12-week survival rate was 63%, and the authors stated that their findings in this pilot study should be investigated in further randomized controlled studies.

After the preemptive approach, with promising results, was introduced, studies comparing preemptive and empirical approaches were performed, with conflicting results. Cordonnier et al.²⁸ in their study in 2009, comparing empirical treatment with preemptive approach analyzed the outcome of 293 hematological malignancy patients (150 in the empirical treatment arm and 143 in preemptive approach) with febrile neutropenia. Although they were able to show that preemptive treatment was non-inferior to empirical treatment in terms of survival in the analysis performed in all patients, the sub-group analysis of patients receiving induction chemotherapy showed that empirical approach was associated with a better survival outcome. Therefore, the authors suggested that empirical antifungal treatment may result in higher survival rates than would preemptive treatment among patients receiving induction chemotherapy.

In 2010, Girmenia et al.,²⁹ used a clinically driven diagnostic approach in selected neutropenia episodes. At baseline, three blood cultures were performed. If the patient had 4 days of persisting or relapsing fever or other clinical findings possibly related to an IFI, an intensive diagnostic work-up (IDWU), including GM for 3 days, chest CT and other examinations were conducted. Overall, 49 IFIs were diagnosed during 48 episodes (21.8%). Diagnostic driven therapy was administered to 48 patients with IFIs; one patient with zygomycosis died without treatment. Only one patient received empirical therapy. The authors stated that this approach provided effective antifungal control and reduced the exposure to unnecessary antifungal treatment. However, they stressed that non-*Aspergillus* infections may be a problem and in order to use this approach, the early availability of microbiologic and radiologic examinations is mandatory.

In 2011, Pagano et al.³⁰ analyzed the outcomes of empirical and preemptive approaches on 397 high-risk hematological malignancy patients in real life setting. Proven/probable IFIs were significantly lower in patients treated with empirical therapy (7.4%) as compared to those treated preemptively (23.7%). The invasive fungal disease-attributable death rate was significantly lower ($p=0.002$) in the empirical therapy group (1 case; 7.1%) than that in the pre-emptive therapy group (11 cases; 22.5%). The authors demonstrated that empirical therapy reduced the IFI-attributable mortality and increased survival probability of patients as compared to preemptive approach. The authors emphasized that the empirical approach is likely to guarantee a better outcome in hematological patients despite the risk of overtreatment, and empirical approach is probably the best treatment of choice when microbiological and radiological support is lacking. They also stated that pre-emptive therapy should be reserved for centers where a risk-based approach is feasible, using clinical rules and intensive diagnostic techniques to identify patients with IFI at a very early stage of disease. This study is the most important one in favour of empirical treatment against the pre-emptive approach, as it showed a survival benefit in those treated with empirical treatment.

Although empirical treatment is costly when compared to a pre-emptive approach, given the survival

benefits mentioned in two studies, one in a real life setting and the other in a randomized controlled trial, empirical treatment should be started in high-risk febrile patients with hematological malignancies, who present with fever without an apparent focus for more than 3 days after a broad spectrum antibiotic treatment, while screening with available diagnostic tools are going on. As there are insufficient data supporting the pre-emptive approach, the European Conference on Infections in Leukaemia (ECIL)- 4 guideline has no recommendation for the pre-emptive approach. The grades of recommendation for empirical treatment are different in each of the guidelines published by different scientific societies. In the ECIL-3 guideline, the grade of recommendation is BII, in the Infectious Diseases Society of America (IDSA) AI for neutropenia lasting for more than 7 days, and AIII if the risk of IFI is low, and the Study Group for Infections in the Critically Ill Patient of the Spanish Society for Infectious Diseases and Clinical Microbiology SEIMC only recommends empirical therapy in patients with high or intermediate risk of aspergilosis and infections caused by other filamentous fungi.¹⁸

Ideal Antifungal Treatment in Empirical Setting?

An ideal empirical treatment should be effective against fungi most commonly seen in these patients, have a wide-spectrum of activity so that it can be effective in newly emerging species, and should have a favourable safety profile. The antifungal agents used in empirical treatment are polyenes, azoles and echinocandins, though some other antifungals, such as flucytosines are also available.

Several factors should be considered in selecting an antifungal drug (Table 4).³¹

Epidemiology of IFIs is an important factor in selecting the appropriate antifungal agent. Currently *Aspergillus* species are the most common fungi encountered in hematological patients, followed by *Candida* spp., and considering the changing resistance patterns and emergence of new fungi, the antifungal agent used should have a broad spectrum. Amphotericin B has a broad spectrum of fungicidal activity against *Candida* spp., *Aspergillus* spp.,

Table 4. Factors to be considered when selecting an antifungal agent for empirical treatment			
Epidemiology of invasive fungal infection (IFI)	Candida		
	Aspergillus	Other filamentous fungi	
Spectrum of the antifungal	Candida	Aspergillus	Other filamentous fungi
Polyene	+++	+++	+++
Voriconazole	+++	+++	++
Caspofungin	+++	+++	-
Type of activity	Yeast	Filamentous fungi	
Polyene	Fungicidal	Fungicidal	
Voriconazole	Fungistatic	Fungicidal	
Caspofungin	Fungicidal	Fungistatic	
Clinical experience	Efficacy against Aspergillus	Evidence for breakthrough aspergillosis and mucormycosis	
Polyene	+++	-	
Voriconazole	+++	+	
Caspofungin	++	+	
Severity of infection	For empirical treatment select the antifungal agent with the highest efficacy and the broadest spectrum of action		
Prophylaxis with triazole or candidin	In case of suspected IFI begin with liposomal amphotericin B		

Cryptococcus spp., Fusarium spp., Mucorales, and endemic fungi. Whereas, azoles have fungicidal activity only against Aspergillus spp., and echinocandins only against Candida. Voriconazole and liposomal amphotericin B have shown higher efficacy against Aspergillus infections in large randomised controlled trials^{32,33} whilst caspofungin has only a salvage indication in aspergillosis. Breakthrough Aspergillus and Mucorales infections have been documented during caspofungin and voriconazole treatment^{31,34} but not during amphotericin B treatment.

Polyenes are the oldest antifungal drugs, introduced in the 1950s, and lipid formulations of amphotericin B have less nephrotoxicity and infusion-related reactions as compared to conventional amphotericin B, with liposomal amphotericin B showing the

greatest reduction in infusion related adverse events and nephrotoxicity. As stated amphotericin B has a broad spectrum of fungicidal activity against common and emerging fungi, and has been used for over six decades with no documented acquired resistance.

Azoles, especially newer triazoles, have a broad spectrum of activity against fungal pathogens, and voriconazole is generally considered first line therapy for aspergillosis. However, drug toxicity, drug interactions, resistance to Candida and Aspergillus and emergence of the mucormycetes are of concern.

Echinocandins have a good safety profile and are highly effective against Candida infections; they are now recommended as the primary treatment option for candidiasis. However, they do not have ac-

Table 5. In vitro susceptibility of fungal species to antifungal agents by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology³¹

			Liposomal amphotericin B	Amphotericin B	Caspofungin	Itraconazole	Voriconazole	Posaconazole
Yeasts (MIC range µg/ml)	Candida species	<i>C. albicans</i>	0.015-0.12	0.06-1.0	0.06-0.25	0.06-0.5	0.06-0.25	0.06-0.5
		<i>C. glabrata</i>	0.5-1.0	0.125-2.0	0.125-1.0	0.5-4.0	1.0-4.0	0.5-4.0
		<i>C. tropicalis</i>	0.25-1.0	0.125-1.0	0.125-1.0	0.125-0.5	0.06-0.5	0.06-0.5
		<i>C. krusei</i>	0.5-2.0	0.25-2.0	0.06-1.0	0.5-4.0	0.5-2.0	0.5-2.0
		<i>C. parapsilosis</i>	0.5-1.0	0.125-1.0	0.5-2.0	0.125-1.0	0.06-0.5	0.03-0.125
	Other yeasts	<i>Saccharomyces cerevisiae</i>	0.03-0.06	0.5-1.0	1.0-2.0	1.0-4.0	0.125-0.5	0.5-1.0
		<i>Trichosporon inkin</i>	0.03-0.06	0.5	4.0-8.0	0.03-0.5	0.01-0.03	0.25-0.5
		<i>Trichosporon asahii</i>	0.01-0.03	1.0-2.0	4.0-8.0	0.03-0.5	0.03-0.06	4.0-8.0
Moulds (MIC range µg/ml)	Aspergillus species	<i>A. fumigatus</i>	0.5-2.0	0.5-2.0	0.25-1.0*	0.5-1.0	0.25-1.0	0.5-1.0
		<i>A. terreus</i>	2.0-4.0	2.0-4.0	0.125-1.0*	0.5-1.0	0.25-1.0	0.125-0.5
		<i>A. flavus</i>	1.0-4.0	1.0-4.0	0.25-1.0*	0.5-2.0	0.5-2.0	0.125-0.5
		<i>A. niger</i>	1.0-2.0	0.5-4.0	0.25-1.0*	2.0-4.0	0.5-2.0	0.25-0.5
	Other moulds	<i>Fusarium oxysporum</i>	0.03-0.5	1.0-4.0	NA	1.0-8.0	4.0->8.0	0.125
		<i>Fusarium solani</i>	4.0-8.0	4	NA	4.0-8.0	NA	1
		<i>Mucor spp.</i>	0.03-0.5	0.5-1.0	NA	4.0-8.0	NA	2.0-4.0
		<i>Penicillium spp.</i>	0.5-1.0	0.5-1.0	NA	0.5-8.0	2.0->8.0	0.5
		<i>Rhizomucor spp.</i>	0.3-0.125	0.25-1.0	NA	NA	NA	1.0-4.0
		<i>Rhizopus spp.</i>	1.0-4.0	1.0-4.0	NA	NA	NA	2.0-4.0
<i>Scedosporium apiospermum</i>	1.0-2.0	2.0-4.0	NA	2.0-4.0	2.0->8.0	0.5-2.0		

*MEC range µg/ml
NA = No Activity (MIC or MEC range >8 µg/ml)
Adapted from Lass-Flörl et al, 2008

tivity against non-Candida yeasts or against *Cryptococcus*, *Fusarium* and *Scedosporium* spp. or mucormycetes, and have fungistatic activity against *Aspergillus* spp., the most frequently encountered species in hematology patients.

Despite their potential toxicity, polyenes remain useful in the empiric treatment of IFIs because of their long track record, broad spectrum of activity and low rates of resistance. Furthermore, they are active against Mucorales.

With prolonged use of antifungal drugs, particularly azoles and echinocandins, in prophylactic and empirical settings in immunocompromised individuals, clinicians should anticipate breakthrough infections. Whenever possible, accurate identification of the infecting organism is critical for the optimal management of breakthrough IFIs.

The antifungal spectrum of antifungal agents frequently used in clinical practice is given in Table 5.³⁵

A diagnostic-oriented approach requires the availability of diagnostic tests with a rapid turnaround and the full cooperation and compliance of all parties involved, including clinicians, microbiologists, radiologists, nurses, or pharmacists, as well as a strict adherence to minimum standards of diagnosis.

In light of the literature and past experiences, we recommend empirical treatment in high-risk patients with hematological malignancies, bearing in mind that the patient should be meticulously examined and monitored to find the causative agent. The best antifungal therapy choice should consider both antimicrobial spectrum of the agent, and possible drug toxicities in order to tailor the treatment approach in these patients with multiple co-morbidities and concomitant drug usage.

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