# Recommendations for the treatment of invasive fungal infection caused by filamentous fungi in the hematological patient

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## ABSTRACT

Antifungal treatment in the hematological patient has reached a high complexity with the advent of new antifungals and diagnostic tests, which have resulted in different therapeutic strategies. The use of the most appropriate treatment in each case is essential in infections with such a high mortality. The availability of recommendations as those here reported based on the best evidence and developed by a large panel of 48 specialists aimed to answer when is indicated to treat and which agents should be used, considering different aspects of the patient (risk of fungal infection, clinical manifestations, galactomanann test, chest CT scan and previous prophylaxis) may help clinicians to improve the results.

**Key words: Invasive fungal infections, hematological patients, amphotericin B, voriconazole, posaconazole, echinocandins.**

## Recomendaciones para el tratamiento de las infecciones fúngicas invasoras causadas por hongos filamentosos en pacientes hematológicos

## RESUMEN

El tratamiento antifúngico del paciente hematológico ha alcanzado una gran complejidad con la llegada de nuevos antifúngicos y pruebas diagnósticas que han dado lugar a diferentes estrategias terapéuticas. La utilización del tratamiento más adecuado en cada caso es fundamental en infecciones con tanta mortalidad. La disponibilidad de recomendaciones como éstas, realizadas con la mejor

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evidencia por un amplio panel de 48 expertos, en las que se intenta responder a cuándo está indicado tratar y con qué hacerlo considerando diferentes aspectos del paciente (riesgo de infección fúngica, manifestaciones clínicas, galactomanano, TC de tórax y profilaxis realizada), puede ayudar a los clínicos a mejorar los resultados.

**Palabras clave: infección fúngica invasora, paciente hematológico, anfotericina B, voriconazol, posaconazol, equinocandinas.**

## RATIONALE

Antifungal treatment in the hematological patient has changed considerably in the past two decades with the advent of new antifungal agents and diagnostic tests, which have expanded the potential therapeutic strategies. From the empirical, almost exclusive, use of amphotericin B deoxycholate (AmB) in the last two decades of the XX century has evolved at the current use, either empirically or as a preemptive therapy, of other drugs, such as lipid formulations of amphotericin B, candins and azoles of equal or superior efficacy, less toxic and better tolerated.

The rationale for empirical therapy is based on two studies of AmB carried out in the 80's showing a reduction in the incidence and mortality of invasive fungal infection (IFI)[1,2]. This indication has been later extended to lipid formulations of amphotericin B and caspofungin[3-9]. At the present time, empirical treatment is recommended in hematological patients with high or intermediate risk of IFI, who present fever witout an apparent focus for more than 3 days after a broad spectrum antibiotic treatment[10-12]. However, the grades of recommendation are different in each of the guidelines published by different scientific societies. In the ECIL-3 guideline, the grade of recommendation is BII[12], in the IDSA is AI for neutropenia lasting more than 7 days and AIII if the risk of IFI is low[11], and the SEIMC only recommends empirical therapy in patients with high or intermediate risk of aspergilosis and infections caused by other filamentous fungi[10].

The concept of preemptive therapy (administration of antifungals in patients with a diagnosis of probable fungal infection based on a positive galactomannan test or the presence of a compatible image on the chest or paranasal sinus computed tomography [CT] scan) was developed in 2005[13], with the aim of reducing the number of patients who receive empirical treatment, maintaining the same earliness[14,15]. However, this objective is not always achieved[16-18] due to the delay in having available laboratory results, the relatively low sensitivity of the galactomannan antigen (AGA) in some circumstances[19-23] and the low specificity of the radiological images[24], among other reasons.

## OBJETIVE

The development of these new antifungal agents, the better knowledge of sensitivity and specificity of different diagnostic tests and the identification of other risk factors for IFI (individual genetic predisposition, iron overload, comorbidity, etc.) have increased the complexity of antifungal prophylactic and therapeutic regimens in this patient population. The objective of the present document is intended to answer the following questions: a) when starting treatment of IFI caused by filamentous fungi in the hematological patient is indicated? and b) which is the antifungal of choice in each case?

## METHODS

This document has been developed under the auspices of the Spanish Society of Chemotherapy (SEQ) and with the participation of 33 hematologists, 10 specialists in infectious diseases, 4 microbiologists and 1 clinical pharmacologist who work at second- or third-level Spanish hospitals with experience and active clinical practice in the management of the neutropenic patient.

A first draft was initially elaborated, which was thereafter discussed in successive meetings with the participation of an average of 7 hematologists and 2 specialists in infectious diseases in each of them, up to reach a final manuscript, which was reviewed by some experts. Finally, the document of recommendations was approved by all authors.

## RECOMMENDATIONS

**When starting antifungal treatment is indicated?**

The decision to start antifungal treatment can be established according to the following aspects:

1) Risk of IFI.

2) Severe clinical picture or suggestive of IFI.

3) Results of complementary tests: galactomanann, β-glucan and CT scan of the chest or sinuses.

1) *Risk of IFI*

The most important factors in the development of IFI are the level of depression of the cellular immune status and, particularly, the intensity and duration of neutropenia. According to these two parameters, patients can be classified into three main risk groups (figure 1)[10,11]:

a) High-risk: in the presence of profound (absolute neutrophil count < 100/mm$^3$) and prolonged (> 14 days) neutropenia or an important deficiency of cell immunity as a consequence of chemotherapy, radiotherapy, citomegalovirus (CMV) infection, graft-versus-host disease (GVHD) or treatment with corticosteroids, anti-TNF-α agents or alemtuzumab[25-27]. This group includes allogenic stem cell transplantation (SCT) with umbilical cord blood or allogenic HLA-mismatched SCT, allogenic SCT with GVHD, and acute leukemias (myeloid or lymphocytic) and myelodysplastic syndromes during induction, re-induction or rescue therapy.

b) Medium-risk: the duration of neutropenia is typically 7-14 days, and this group includes HLA-matching allogenic SCT

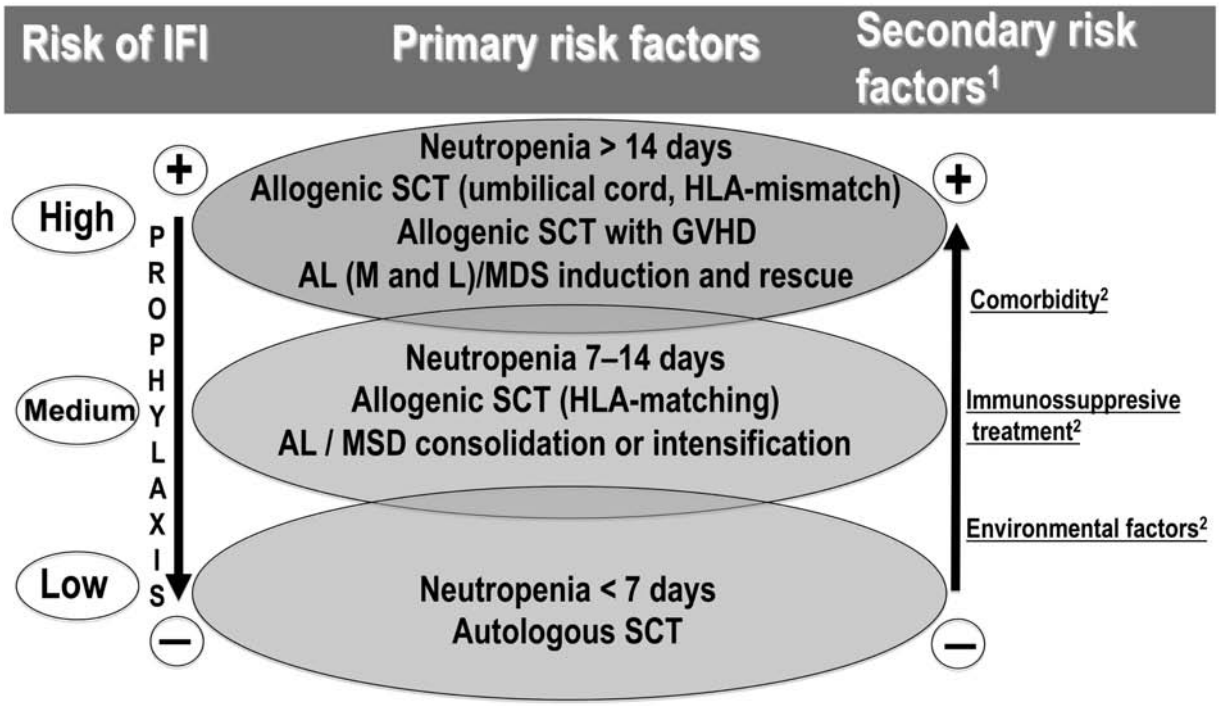


**Figure 1** | **Classification of the risk groups for IFI.**

[1]The presence of one or more of these factors may determine an increase of the risk group;
[2]See table 1. SCT: stem cell transplantation; AL: acute leukemia; GVHD: graft-versus-host disease; M: myeloid; L: lymphocytic; MDS: myelodisplastic syndromes.

and acute leukemias and myelodisplastic syndromes during consolidation or intensification chemotherapy.

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

In recent years, other risk factors for IFI related to comorbidities, immunosuppressive therapy, the level of air pollution and certain genetic predisposition have been identified (table 1)[28-36]. In relation to genetic predisposition, it has been shown the importance of different genetic polymorphisms (mann-binding lectin [MBL], *Toll-like* receptors [TLR4-2], dectin-1, plasminogen, interleukin-10, pulmonary surfactant, etc.)[28-32] but data are still insufficient for establishing recommendations regarding the consideration and systematic detection of these markers and are far from the routine clinical practice. On the other hand, during the last years antifungal prophylaxis protocols adjusted to the risk of infection by molds or filamentous fungi have been generalized[10-12]. However, the final inclusion of a particular patient in one or another risk group depends not only of the presence of main risk factors, but also of other secondary factors (table 1) and whether or not the patient has received or is being receiving prophyaxis against filamentous fungi. The assessment of each of these aspects can make us change the initial risk group defined according to criteria of figure 1. In relation to antifungal prophylaxis, it should be born in mind that a considerable percentage of patients treated with oral itraconazole, posaconazole and, to a lesser extent, voriconazole may have subtherapeutic levels of the drug[37,38].

2) *Severe clinical picture or suggestive of IFI*

The presence of severe clinical manifestations or highly compatible with IFI caused by filamentous fungi, such as persistent cough, hemoptysis, pleuritic pain or dyspnoea should be considered at the time of starting antifungal treatment in the high-risk hematological patient especially in the presence of a lack of response to antibiotic treatment and a progressive increase of C-reactive protein (CRP) or procalcitonin[39-42]. The presence of respiratory failure, criteria of severe sepsis, infection of the central nervous system or uncontrolled immunosuppression further increases the probability of IFI caused by filamentous fungi and, therefore, the possible need of empirical treatment with broad-spectrum antifungals.

3) *Complementary tests*

The positivity of AGA (> 0.8 ng/mL or > 0.5 ng/mL in two

**Table 1** Other risk factors of IFI.

| Comorbidity | Immunossuppressive treatment | Environmental factors |
|---|---|---|
| Age > 65 years | Prolonged corticosteroid treatment | Building works in the neighboring |
| Advanced disease | Alemtuzumab | Rooms without HEPA filters |
| Previous invasive fungal infection | Citarabine at high doses | |
| Iron overload | Anti-TNF agents | |
| Metabolic acidosis | High doses of total body irradiation | |
| Non-controlled hyperglycemia | | |
| Cytomegalovirus infection | | |
| Infection caused by a respiratory virus | | |
| Chronic obstructive pulmonary disease (COPD) | | |
| Renal failure | | |
| Liver failure | | |
| Malnutrition | | |
| Genetic polymorphisms (MBL, TLR4-2 ...) | | |

**Table 2** Indications of antifungal treatment.

| Clinical situation | Type of treatment |
|---|---|
| a) Positive galactomanann test or CT scan of the chest or sinuses compatible with fungal infection | Preemptive |
| b) Patient with fever that persists for > 3-5 days (high-risk)[1] or > 5-7 days (medium-risk)[1] after the onset of antibiotic treatment with negative microbiological tests[2,3] | Empirical |
| c) Presence of an infection focus and evidence of proven or probable IFI. | Directed |

[1]See risk classification in table 1.
[2]In case of significant clinical deterioration, antifungal treatment should be immediately started independently of the duration of fever.
[3]Progressive increase of PCR or procalcitonin may be useful for deciding empirical treatment.

consecutive assays) and the presence of some radiological images, even in the absence of clinical manifestations, may be the first signs of IFI and justify to consider starting active antifungal treatment against *Aspergillus* spp. (preemptive therapy)[43-45].

In relation to AGA, it is known that in animal models of aspergillosis, a direct relationship between serum AGA levels and the number of colony-forming units of *Aspergillus* per gram of lung tissue has been observed[43]. However, the sensitivity of AGA test may be lower than the desirable sensitivity in some cases, such as: a) during the days prior to the onset of fever and on the first day of fever[14], b) infections caused by *A. fumigatus*, which is the most prevalent species, due to a lower quantity of galactomannan as a cell wall component[19,20]; c) in patients receiving prophylaxis, in which overall fungal burden may be decreased[22]; and d) in patients with less profound neutropenia (> 100/mm$^3$) in whom fungus is developed more slowly and with more difficulty[23].

On the other hand, chest CT demonstration of halo or the reverse halo sign suggestive of aspergillosis and mucormycosis, respectively, is not patognomonic and may be observed in other infectious (bacterial, mycobacterial, viral or parasitic) and non-infectious (neoplasms, vasculitis, amyloidosis, sarcoidosis, etc.) diseases and, for this reason, assessment of the individual clinical context is essential[24].

According to all these aspects, the beginning of antifungal treatment in the hematological patient at risk of IFI should be considered at any time in the following conditions (table 2):

a) the AGA test is positive or CT scan of the chest or the sinues is compatible with fungal infection (*preemptive treatment*).

b) in case of persistent fever, absence of clinical improvement, and negative results of microbiological tests despite the administration of antibiotic treatment for more than 3 days (high risk patisnt) or more than 5 days (medium risk patients)(*empirical treatment*). When the patient's clinical deterioration is significant, antifungal treatment should be started independently of the duration of fever. The progressive increase of PCR or procalcitonin, despite antibiotic treatment, may be useful to make the decision of starting empirical treatment[39-42].

c) in the presence of an infection focus and evidence of proven or probable IFI (*directed treatment*).

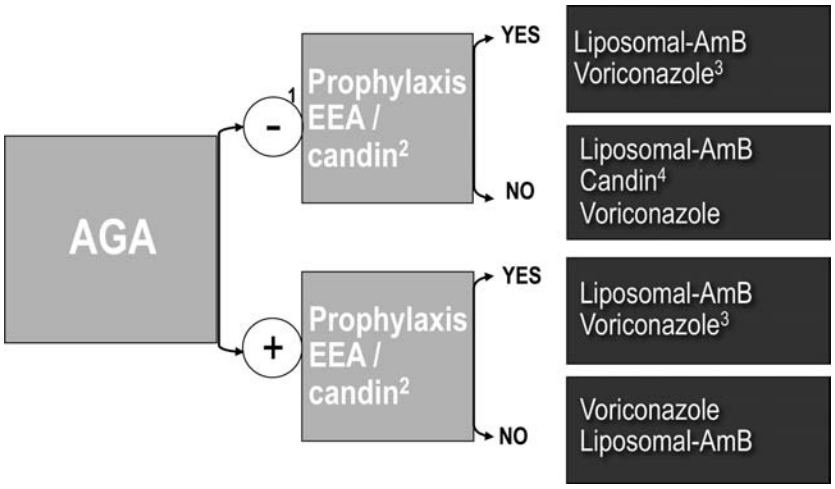


**Figure 2** | **Selection of the antifungal agent according to galactomanann antigen (AGA) and prophylactic antinfungal regimen.**

AGA: galactomanann antigen; EEA: extended-spectrum azole (voriconazole and posaconazole)
[1]AGA negative or not available.
[2]Micafungin is the only candin with indication for prophylaxis.
[3]Consider using voriconazole if the patient is receiving a prophylaxis with a candin.
[4]If clinical picture and/or imaging studies are compatible with IFI caused by filamentous fungi, it is recommended not to use candin (caspofungin is the one with indication in empiric) in monotherapy.

**Which antifungal agent should be used?**

The selection of the antifungal agent in each case depends mainly on the result of AGA and the type of prophylaxis that the patient has received. According to these two criteria, four groups of patients can be identified (figure 2):

1) If the AGA test is negative or unavailable and the patient has received prophylaxis with an extended-spectrum azole (EEA) or a candin, the risk of aspergillosis decreases, but the possibility of infection by other filamentous fungi especially Mucor persists, due to the lack of activity of both candins and voriconazole against *Mucor* spp. Posaconazole is active against some Mucorals but adequate serum concentrations are frequently not reached[37,46-49] In these circumstances, liposomal amphotericin B (L-AmB) is the antifungal of choice because of its broadest spectrum of activity (*Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., *Fusarium* spp. Mucorals and endemic fungi) and is the first option for the treatment of mucormycosis[50-52]. If the patient has received prophylaxis with a candin, L-AmB or voriconazole can be used for empirical treatment.

2) If the AGA test is negative or unavailable and the patient has not received prophylaxis with an EEA or a candin, infection can be caused either by *Candida* spp. (especially *C. glabrata* or *C. krusei* if prophylaxis with fluconazole was given) or *Aspergillus* spp. In this case, L-AmB, a candin drug or voriconazole are included in the empirical antibiotic regimens. The three options are equally valid[4-7]. However, if results of the CT scan are compatible with IFI, it is advisable to give priority to voriconazole or L-AmB in detriment to capufungin because the antifungal spectrum of this agent against filamentous fungi is narrower, the *in vitro* fungistatic activity and in vivo seems to be less effective against *Aspergillus* (caspofungin 30-40% vs. L-AmB and voriconazole 40-50%)[53-57] and for which the development of breakthrough aspergillosis has been described[58,59].

3) If the AGA test is positive and the patient has received prophylaxis with an EEA or a candin, there is a high probability of aspergillosis due to failure of the agents used for prevention therapy[37,48,58,59]. In the case of prophylaxis with an EEA, L-AmB would be the first therapeutic option because this fact does not seem to affect the clinical efficacy of amphotericin[60]. If a candin drug has been used for prophylaxis, voriconazole and L-AmB are the therapeutic options.

4) If the AGA test is positive and the patient has not received prophylaxis, the therapeutic options include voriconazole and Anfo B-L[55-57].

In relation to formulations of amphotericin B, it should be noted that the conventional formulation is not regarded as a therapeutic option due to its high toxicity. Therefore, there are two formulations of amphotericin B to be considered: liposomal formulation and the lipid complex. These two formulations have some important differences that in practice should be taken into account at the time of prescribing these drugs, especially in the immunocompromised patient suffering from a potentially serious infection. In particular, there are evidences of the lower incidence of infusion reactions and nephrotoxicity with the liposomal formulation, probably in relation to the higher stability of the liposome[5,61-63]. This lower incidence is due to the presence in the liposome of cholesterol and phospholipids that are thermostable at the body temperature. These characteristics make liposomal amphotericin B as the amphotericin B of choice[63].

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