Review

Carlos Vallejo[1]
José Barberán[2]

Empirical antifungal treatment: a valid alternative for invasive fungal infection

[1] Servicio de Hematología, Hospital Central de Asturias, Oviedo
[2] Servicio de Enfermedades Infecciosas, Hospital Central de la Defensa Gómez Ulla, Madrid

ABSTRACT

Empirical antifungal therapy refers to initiation of an antifungal agent at the first possible clinical evidence of fungal infection. It is frequently recommended in neutropenic high-risk hematological patients of invasive fungal infection in order to guarantee an early approach. An extensive review is made of therapeutic advances and scientific evidence in this setting. Specific recommendations for use and criteria for selection of antifungal agents are discussed.

Key words: empirical antifungal therapy, hematological patients, invasive fungal disease, amphotericin B, voriconazole, caspofungin.

Tratamiento antifúngico empírico: una alternativa válida para la infección fúngica invasora

RESUMEN

El tratamiento antifúngico empírico consiste en la administración de un antifúngico ante la primera sospecha clínica de infección fúngica. Es frecuentemente recomendado en pacientes hematológicos neutropénicos con alto riesgo de desarrollar una infección fúngica invasora. En este artículo se hace una revisión de los avances terapéuticos y de la evidencia científica del tratamiento empírico y se discuten las recomendaciones de su utilización y los criterios para la selección de fármacos.

Palabras clave: tratamiento antifúngico empírico, pacientes hematológicos, infección fúngica invasora, anfotericina B, voriconazol, caspofungina.

Correspondencia:
Dr. J. Barberán,
Servicio de Enfermedades Infecciosas, Hospital Central de la Defensa Gómez Ulla,
Gta. Del Ejército s/n, E-28047 Madrid, España.
Tel.: +34 91 394 1508;
fax: +34 91 394 1511,
E-mail: josebarberan@teleline.es

Fungal infections have very serious implications and are most likely to affect patients with a hematological malignancy. Hematological malignancy patients frequently develop invasive fungal infection (IFI) caused by filamentous fungi and may be considered as subjects to the risk prototype[1,2]. The intensity and duration of neutropenia, the diagnosis of acute leukemia, and the severe impairment of lymphocytic activity are classic predisposing factors for IFI, and are the basis for risk stratification into high, intermediate and low risk groups. High-risk criteria include profound (absolute neutrophil count < 100/mm^3) and prolonged (> 14 days) neutropenia after induction or rescue chemotherapy of the acute leukemias or in the context of immunodeficiency secondary to graft-versus-host disease (GVHD) after allogenic stem cell transplantation (SCT) and its treatment (corticosteroids, anti-TNF-α antibodies, alemtuzumab or anti-thymocyte globulin –ATG-) or to a cytomegalovirus infection[3-5]. In the medium-risk group are included the neutropenia of 7-14 days or after consolidation or intensification chemotherapy of patiens undergoing acute leukemia. The low-risk category is characterized by neutropenia of < 7 days or during autologous SCT[6].

However, factors that may cause patients framed in a particular risk group to move to a higher category are likely to be considered in the forthcoming years. In this respect, individual predisposition to develop a fungal infection has been recognized and in recent years, multiple studies have provided evidence of deficiencies of the innate immune system that reduce the efficacy of natural defence mechanisms against IFI, especially in relation to some genetic polymorphisms in the mannan-binding lectin (MBL) pathway, toll-like receptors (TLR4-2) and dectin-1 that allow fungal identification and phagocytosis, as well as plasminogen, interleukin-10 and surfactant proteins difficulting clearance of inhaled conidia by the alveolar macrophage[7-11]. Iron overload is also an important risk factor for IFI, in particular zygomycosis but also *Aspergillus* infections. Iron is essential for fungal growth and virulence, therefore, a net increase in host iron stores would increase iron availability and enhance fungal growth[12]. Other factors that favor fungal multiplication are advanced age and some comorbidities, such as sustained hyperglycemia, metabolic acido-

Table 1 **Risk factors for the development of invasive fungal infection (IFI)**

Neutropenia / lymphopenia	Individual predisposing conditions	Probability of infection / colonization
High-risk:	**Genetic deficiency of innate immune status:**	Absence of HEPA filter
Neutropenia of < 100/mm3 and > 14 days	MBL	Local prevalence of IFI
Lymphopenia/functional impairment of lymphocytes	TLR4-2	History of IFI
• Prolonged treatment with corticosteroids	Dectin-1	Underlying lung diseases
• Anti-TNF, ATG	Plasminogen	
• Alemtuzumab	IL-10	
• CMV infection	Pulmonary surfactant	
Medium-risk:	**Iron overload**	
Neutropenia 7-14 days	**Comorbidity:**	
Low-risk:	Sustained hyperglycemia	
Neutropenia < 7 days	Metabolic acidosis	
	Structural pulmonary disease	

TNF: tumor necrosis factor; ATG: anti-thymocyte globulin; MBL: mannan-binding lectin; TLR: toll-like receptors; IL: interleukin; HEPA: high efficiency particulate air.

sis that stimulates the release of iron from transferrin, and structural lung diseases allowing progression of conidias[13,14]. Moreover, the probability of inhalation of fungal spores or pulmonary fungal colonization is related to the absence of HEPA filters in patients rooms, local prevalence of IFI (construction dust, weather conditions –warm, dry climates-), history of IFI, and underlying lung diseases (e.g., chronic obstructive pulmonary disease [COPD]) (table 1)[14,15].

Empirical antifungal therapy is the earliest approach when an IFI is suspected and is recommended in hematological patients with high or medium risk of IFI presenting with fever without focus for more than 3 days after a broad-spectrum antimicrobial treatment[6,16]. Two studies published in the 80's showed a reduction in the incidence and mortality of IFI in a small clinical series of patients treated with amphotericin B deoxycholate[17,18]. Thereafter, by the end of the 90's, the new antifungal agents, --amphotericin B colloidal dispersion (ABCD), liposomal amphotericin B, and caspofungin (but not voriconazole)--, obtained approval for the indication of empirical treatment according to data of comparative studies, most of them with a double blind design, conducted in different risk groups of patients[19-25].

In 2005 with the publication of the study of Maertens and colleagues[26], the concept of preemptive therapy (administration of antifungals in patients diagnosed of probable fungal infection based on some microbiological [galactomannan testing] or radioimaging [chest computed tomography, CT] data) was developed, with the purpose of reducing unnecessary empirical treatments while maintaining early and effective antifungal control. In this study, 41 episodes of febrile neutropenia were qualified for empirical antifungal therapy but only 9 episodes were treated preemptively, and the treatment algorithm with screening for circulating galactomannan and early use of thoracic CT scanning for the detection of invasive aspergillosis failed to identify non-*Aspergillus* infections in 3 cases. However, survival at 3 months was only 63% and, in daily practice, the use of this strategy delays initiation of treatment in 3 or 4 days[26]. Subsequently, two studies using a methodology similar to that of Maertens et al.[26] demonstrated the effectiveness and a reduced antifungal use with the preemptive approach[27,28]. Preemptive therapy mainly relies on the galactomannan assay and chest CT findings suggestive of IFI. However, some consideration should be made regarding the usefulness of galactomannan testing and chest CT scanning for this therapeutic strategy. With regard to galactomannan, there is a direct relationship between galactomanann antigen levels and *Aspergillus* burden (cfu/g lung tissue), which indicates that when results for galactomannan antigenemia are positive, the diagnosis is definitive and invasive aspergillosis is well established[29]. In addition, galactomannan testing has a low sensitivity in the following cases: 1) infections caused by *Aspergillus fumigatus*, which is the most prevalent species, due to a lower quantity of galactomannan released[30,31]; 2) patients receiving prophylactic antifungal drugs as the overall fungal burden may be decreased with the preventive approach[32]; 3) non-severely neutropenic patients (> 100 polymorphonuclear neutrophils [PNM]/mm^3) because fungal development is less extensive and systemic than in severely neutropenic patients (< 100 PNM/mm^3)[33]; and 4) during the days prior to the onset of fever and on the first day of fever, with the subsequent delay in starting antifungal treatment[27]. On the other hand, chest CT demonstration of halo (*Aspergillus*) or the reverse halo sign (mucormycosis) used as radiological markers for preemptive therapy, are not patognomonic and may be observed in a large number of infectious (bacterial, mycobacterial, viral or parasitic) and non-infectious (neoplasms, vasculitis, amyloidosis, sarcoidosis, etc.) diseases[34].

Three studies of preemptive therapy in the management of fungal infection have been published in which the promising results reported by Maertens el al.[26] were not obtained. In a prospective randomized controlled trial, Hebart and co-workers[35] compared PCR-based preemptive therapy (group A) and empirical liposomal amphotericin B treatment (group B),

showing that a higher percentage of patients in group A (57%) than patients in group B (36.7%) received antifungal therapy ($P < 0.0001$) and no differences in mortality (16%). In an open-label, randomized non-inferiority trial, Cordonnier et al.[36] have compared an empirical antifungal strategy with a preemptive one in high-risk neutropenic patients using a galactomannan index ≥1.5 as a positive result and a chest CT if the findings of chest radiograph were normal. Preemptive treatment increased the incidence of invasive fungal disease, without increasing mortality, and decreased the costs of antifungal drugs but empirical treatment showed better survival rates for patients receiving induction chemotherapy. Finally, in the study of Pagano and associates[37], that evaluated the impact of empirical versus galactomannan-based preemptive antifungal approach on the clinical outcome of neutropenic high-risk hematological patients, the incidence of invasive fungal diseases and the invasive fungal disease-attributable death rate were significantly lower in patients treated with the empirical antifungal therapy than in patients treated with the preemptive approach. In summary, preemptive antifungal treatment requires a complex hospital logistic process, begins later (at least 3-4 days after empirical antifungal treatment), a greater number of proven fungal infections and a lower number of possible fungal infections are treated, but the risk of death or unfavorable outcome increases[37]. In contrast, empirical antifungal therapy starts earlier, the probability to actually treat a fungal infection is lower, with risk of overtreatment and increased health care costs, but the probability of poor clinical evolution and death is lower (table 2)[19-24].

Given that an IFI is present in less than 10% of patients receiving empirical antifungal treatment, the indication of empirical therapy depends on the likelihood that patients actually have a fungal infection. In this respect, serial measurements of some biomarkers, such as C-reactive protein and procalcitonin[38-41], and the severity of illness may help to establish a definitive diagnosis of IFI. The disadvantages of empirical antifungal therapy are the toxicity of drugs, the development of resistances, and costs[16].

With respect to resistances, unlike antimicrobials, the importance will be at the long-term but not in an individual patient as no antifungal pressure occurs in the absence of fungi. The level of recommendation of empirical antifungal therapy vary according to the different guidelines, with a level of evidence rating B-II for update of the European Conference on Infections in Leukemia (ECIL-3) (level A-I for liposomal amphotericin B and caspofungin)2, A-I for neutropenic episodes of more than 7 days duration and A-III if the risk of IFI is low for the Infectious Disease Society of America (IDSA)[16], and for aspergillosis and other filamentous fungi infections in patients in the high- or medium-risk groups according to the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)[6].

Amphotericin B deoxycholate has been the 'gold standard' of empirical antifungal treatment for more than three decades. However, multiple studies carried out later have identified other antifungal agents with the same efficacy and higher tolerability, such as lipid forms of amphotericin and caspofungin and, among which, voriconazole can also be included according to some clinical guidelines, although the non-inferiority rate was not achieved in the comparative pivotal trial[6,16,19-24]. Different factors should be considered for the choice of the antifungal agent for empirical therapy, including 1) epidemiology of IFI, 2) spectrum of antifungals, 3) type of activity, 4) clinical experience, 5) severity of infection, and 6) use of previous prophylactic treatment (table 3).

Table 2 Empirical versus preemptive antifungal therapy

Empirical treatment	Preemptive treatment
Earliness	Initiation 3-4 days after empirical therapy
Lower probability of poor clinical evolution and death	Higher probability of poor clinical evolution or death
Overtreatment	Fewer unnecessary treatments
Higher health care costs	Complex logistic process

In relation to the epidemiology, IFI has a high incidence in the hematological malignancy patient and is the first cause of death. Moreover, IFI are frequently underdiagnosed as shown in a study in which autopsy-proven IFI in patients with hematological malignancies was evaluated[42]. In this study, IFIs were identified in 31% of autopsies and most IFIs (75%) were not diagnosed antemortem. The main causative fungi are *Aspergillus* spp. followed by *Candida* spp., although an increase in other species especially *Mucor* that accounts for 10% of isolates in some series has been reported[43-45]. Among antifungals used for empirical treatment, including voriconazole, amphotericin B has a broad spectrum of activity against *Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., *Fusarium* spp., Mucorales, and endemic fungi[44,46]. Amphotericin B has fungicidal activity against *Candida* spp. and *Aspergillus* spp., whereas azoles are only fungicides against *Aspergillus* spp., and echinocandins against *Candida*[46]. Clinical experience has shown a higher efficacy of voriconazole and liposomal amphotericin B as compared with caspofungin for *Aspergillus* infections[47-51] and the development of breakthrough aspergillosis and mucormycosis in high-risk hematological patients under treatment with caspofugin[45,52-54] and azoles especially in prophylactic treatment[45,55-58]. In patients with very severe infections, high priority should be given to the most effective agent and with the broadest spectrum of activity, whereas toxicity and drug interactions should also be considered in the management of less severe infections[16]. In relation to previous prophylaxis[16], if the patient is being treated with a triazole or a candin antifungal agent, switching to liposomal amphotericin B seems advisable because of the evidence of other emerging filamentous fungi different than *Aspergillus*[2,45], and breakthrough fungemia with candins[45,52-54] and secondary to inadequate serum levels of azoles (voriconazole and posaconazole) when given by the oral route[45,55-57]. On the other hand, it has been shown that prior treatment with any azole does not impact on response in pa-

Table 3 **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**
Amphotericin B	+++	+++	+++
Voriconazole	+++	+++	++
Caspofungin	+++	+++	-
Type of activity	**Yeasts**		**Filamentous fungi**
Amphotericin B	Fungicidal		Fungicidal
Voriconazole	Fungistatic		Fungicidal
Caspofungin	Fungicidal		Fungistatic
Clinical experience	**Efficacy against *Aspergillus***		**Breakthrough aspergillosis and mucormycosis**
Amphotericin B	+ + +		-
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 candin	In case of suspected IFI begin with liposomal amphotericin B		

tients subsequently treated with amphotericin B for confirmed IFI[59].

We conclude that at the present time, despite the availability of diagnostic tests for IFI, empirical antifungal therapy continues to be a valid first-line option in the management of IFI in hematological patients and, although carries the possibility of overtreatment, remains the most effective because implies early commencement of treatment. The use of empirical antifungal therapy according to the guidelines should not be indiscriminate, but focused primarily on severe high-risk patients. Any of the aforementioned antifungal drugs is appropriate but in severe patients on prophylaxis for filamentous fungi, liposomal amphotericin B would be the first choice agent.

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