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Treatment of invasive fungal infections in high-risk haematological patients: What have we learnt in the past 10 years?

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ABSTRACT

Invasive fungal infection (IFI) caused by filamentous fungi remains a very severe infectious complication in patients with onco-haematological diseases. Last advances in the diagnostic and therapeutic fields, today we know that their contributions are limited. Something similar can be said of clinical trials especially in relation to some changes in the characteristics of the host. The development of promising diagnostic techniques and the relative expansion in the number of antifungal agents has been associated with diversification of therapeutic strategies (prophylaxis with extended-spectrum azoles and preemptive antifungal treatment). However, the low sensitivity of AGA testing in some circumstances, and the potential delay in starting treatment due to logistic reasons, has been reflected by a greater mortality in certain type of patients and a significant increase in the days of treatment. All these circumstances has once again focus attention to the empirical approach as a central strategy in high-risk patients. The objective of this article is to review the clinical experience in the treatment of IFI in onco-haematological patients according to data published in the literature in the last decade and to present a set of recommendations.

Key words: onco-haematological patients, diagnosis, prophylaxis, treatment, liposomal amphotericin B, voriconazole

Tratamiento de las infecciones fúngicas invasoras en pacientes hematológicos de alto riesgo: ¿Qué hemos aprendido en los pasados 10 años?

RESUMEN

La infección fúngica invasora (IFI) por hongos filamentosos (HF) sigue constituyendo una complicación infecciosa muy grave en los pacientes con enfermedades onco-hematológicas. Las últimas aportaciones en el campo del diagnóstico y la terapéutica, hoy sabemos que son limitadas. Algo parecido se puede decir de los ensayos clínicos, en especial por algunos cambios en las características del huésped. La aparición de técnicas diagnósticas esperanzadoras y la relativa ampliación en el número de antifúngicos, dio lugar a una diversificación de las estrategias terapéuticas (profilaxis y tratamiento anticipado). Pero la falta de sensibilidad del AGA bajo algunas circunstancias y el potencial retraso en el inicio del tratamiento por motivos logísticos en su realización, se ha traducido en una mayor mortalidad en determinados tipos de pacientes y en un aumento significativo de los días de tratamiento. Todas estas circunstancias han vuelto a colocar el abordaje empírico como una estrategia central en los pacientes de alto riesgo. El objetivo de este artículo es revisar la experiencia clínica en el tratamiento de las IFI en el paciente onco-hematológico publicada en el curso de la última década y hacer unas recomendaciones en base a ésta.

Palabras clave: paciente oncohematológico, diagnóstico, profilaxis, tratamiento, anfotericina B Liposomal, voriconazol

RATIONALE

Invasive fungal infection (IFI) caused by filamentous fungi remains a very severe infectious complication in patients with onco-haematological diseases, particularly, in allogenic stem cell transplant recipients mostly due to the lack of rapid and highly reliable diagnostic tests allowing an early diagnosis and directed antifungal treatment[1].

Last advances in the diagnostic and therapeutic fields have been the detection of *Aspergillus* galactomannan antigen testing (AGA in 2003) and the introduction of echinocandins in 2001, respectively[2,3]. However, after a decade of clinical experience, today we know that their contributions are limited[4-6]. Something similar can be said of clinical trials especially in relation to some changes in the characteristics of the host (age, risk factors, new immunosuppressive treatments, prophylactic regimens, etc.)[7-9]. In fact, a large body of evidence supporting current decisions regarding antifungal therapy is based on data from observational studies and expert recommendations[10-13].

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In the last decade, the increase in high-risk onco-haematological patients, the development of promising diagnostic techniques and the relative expansion in the number of antifungal agents has been associated with diversification of therapeutic strategies. Among these strategies, prophylaxis with extended-spectrum azoles (EEA) has resulted in a decrease in mortality of high-risk patients and changes in the epidemiological characteristics of IFI[14-19]. However, interactions of azoles with some drugs (chemotherapeutic and immunosuppressive agents) that are increasingly used in this type of patients, as well as difficulties in reaching therapeutic serum concentrations in some clinical situations (mucositis, diarrhoea, etc.) when the drug is administered by the oral route, has prompted the introduction of other antifungal classes in the prophylaxis setting[8,20-23]. On the other hand, based on the possibility of AGA detection, preemptive antifungal treatment has been strongly positioned against empirical treatment, the objective of which was to prevent unnecessary overexposure to antifungals and to reduce the economic cost[24]. However, the low sensitivity of AGA testing in some circumstances, such as in patients receiving prophylaxis with EEA[24-26] and the potential delay in starting treatment due to logistic reasons, has been reflected, according to the experience of some authors, by a greater mortality in certain type of patients and a significant increase in the days of treatment[10]. All these circumstances has once again focus attention to the empirical approach as a central strategy in high-risk patients, as stated in the recommendations of some of the most recent therapeutic guidelines[13,17]. At present, it is accepted that empirical antifungal treatment of the high-risk onco-haematological patient should be started as soon as possible, should offer a broad spectrum of antifungal activity and should be preferably fungicidal with an acceptable toxicity.

The objective of this article is to review the clinical experience in the treatment of IFI in onco-haematological patients according to data published in the literature in the last decade and to present a set of recommendations.

Epidemiological changes of fungal infections

Aspergillus spp. and to a lesser extent *Candida* spp. are the main causative agents of IFIs in the onco-haematological patient. *Mucor* spp. ranks third but its prevalence seems to be increasing as shown by some North American and European studies[1,27,28]. In our country, the incidence of murcomycosis appears to be low and poorly characterized[29], although the occurrence of this infection may be underestimated due to difficulties in establishing a definitive diagnosis[30,31]. It should be noted that invasive zygomycosis may develop in patients exposed to antifungals without activity against these fungi, such as fluconazole, voriconazole or candins, or in those exposed to antifungals with activity but frequently given underdoses, such as the case of posacozalone[29-32].

During this time period, an increase in *Candida* spp. resistant to azoles has also been observed, favoured by the use of these antifungals in prophylaxis or treatment regimens[11,33]. Moreover, secondary resistances of *Aspergillus* spp. to azoles have been reported in some European countries, a fact which has not been confirmed in national studies[34-40]. A similar phenomenon occurred with candins[41,42], although it is possible that resistance may be underestimated because of the lack of sensitivity of *in vitro* techniques, which hampers the correct identification of resistant isolates[41-43].

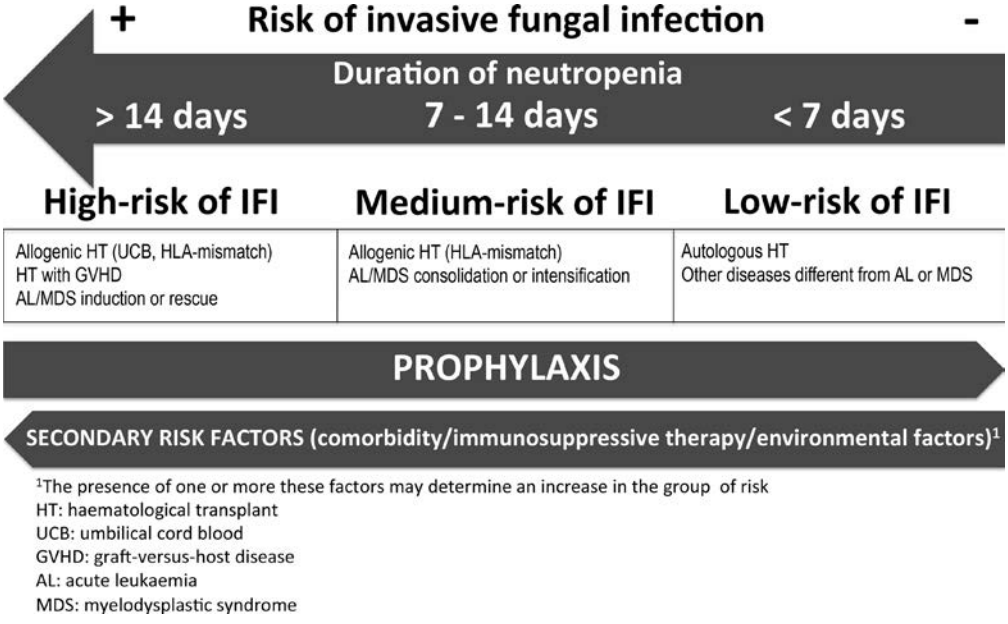


Figure 1 | **Classification of patients according to the risk of invasive fungal infection (IFI)**

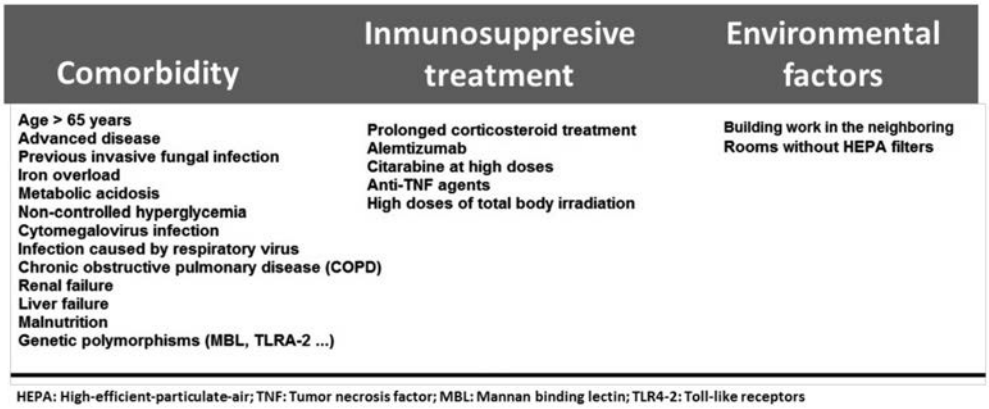


Figure 2 Secondary risk factors of invasive fungal infection

High-risk haematological patient-related changes

With the aim of selecting the most adequate therapeutic strategy, the risk of IFI in onco-haematological patients has been stratified into high-risk, medium-risk and low-risk groups[13,44]. Although profound and/or sustained neutropenia continues to be the main and most frequent risk factor for IFI, the different types of allogenic stem cell transplantation have gain an increasing interest in recent years. Also, changes in the host in association with the use of peripheral blood progenitors, among others, have increase the prevalence and duration of graft-versus-host disease (GVHD) in some groups of patients, who need immunosuppressive treatment and specifically the use of corticosteroids. The association of GVHD and steroids has become one of the main risk factors of IFI in the haematological patient[7,45-48]. In general, the incidence of proven or probable IFI caused by filamentous fungi in haematological patients at risk ranges between 4% and 22%[49], although the extent of the problem may be even greater as shown by a recent study of 1213 autopsies in patients with malignant haematological diseases in whom *ante mortem* diagnosis of IFI was only established in 51% of the cases[4].

Therefore, in the risk assessment of IFI in the onco-haematological patient both primary factors and other aspects related to comorbidities and concomitant treatments (purine analogues, immunosuppressants, mono or polyclonal antibodies, etc.) should be considered. The presence of one or the combination of several factors are determinants to increase the patient's risk category, initially included in the medium-risk or low-risk group[7,14,50]. The design of a large epidemiological and multicentre study would be ideal to develop a *risk score* including all and each individual risk factors of IFI, both primary and secondary, in order to define better which patients may benefit from an earlier antifungal treatment (figures 1 and 2).

Usefulness of diagnostic tools in the high-risk haematological patient

The current diagnostic techniques are neither sufficiently sensitive nor specific to detect early the development of IFI caused by filamentous fungi in high-risk patients; also, research and advances in this field up to the present time have been limited. Culture continues to be the "gold standard" of miocrobiological diagnosis but its reliability for filamentous fungi is very low, and false negative results are common in most cases of IFI[51]. Other disadvantages are the length of time needed for diagnosis and the difficulty in distinguishing between colonization and infection.

AGA detection has become a key test for early diagnosis of invasive aspergillosis. However, the AGA test is not free of false positive and false negative results[24,25,52]. It has been shown that prophylaxis with EEA can reduce the sensitivity of the test up to 30%[24,25]. Also, in a necropsy study of transplant recipients, 49% of patients with proven aspergillosis had various and successive negative AGA tests; it should be noted that in this population non-myeloablative conditioning regimens were used, so that the lower degree of neutropenia may account for the low sensitivity of the test[4,53]. On the other hand, it has been found that the sensitivity of the AGA test varies according to the fungal species[54]. False positive results of the AGA tests have been reported with the use of candins[54,55] and some *Fusarium* spp. (containing galactomannan)[56]. Moreover, in the analysis of the usefulness of the AGA test, some logistic aspects such as the periodicity of the performance of the test at each centre should be considered. In any case, an eventual delay in performing the test and having the results available should not affect the time of starting antifungal treatment in a high-risk patient.

Chest CT demonstration of halo or the reserve halo sign are suggestive of aspergillosis or murcomycosis and, therefore these radioimaging findings are not useful for the differentiation of these entities, and even may be observed in other non-fungal respiratory infections[57-60]. In addition, the presence of radiologically visible pulmonary lesions is frequently a sign of advanced disease.

In summary, diagnostic techniques currently available in the hospitals are not sufficiently early or reliable to be considered

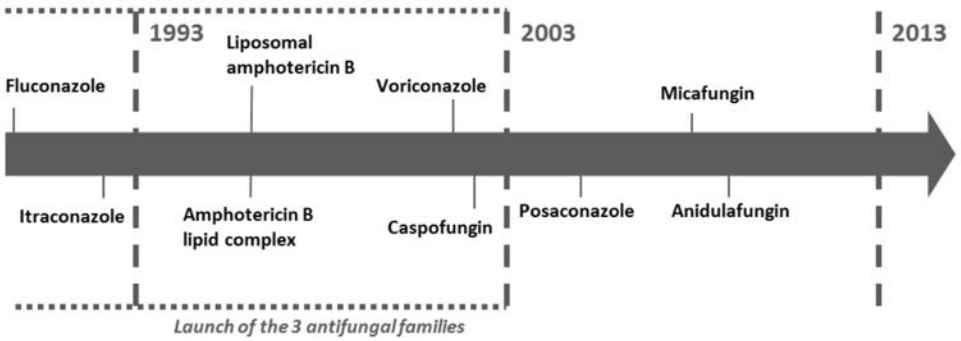


Figure 3 | **Time course in the development of antifungal agents.**

Table 1 | **Efficacy according to the clinical experience (IV therapies)[49,101].**

Efficacy	*Aspergillus*	Zygomycetes	*Non-albicans Candida*
L-Amph B	+ + +	+ + +	+ + +
Echinocandins	+ / + +	+ / -	+ + +
Voriconazole	+ + +	-	+ +

L-Amph B: Liposomal amphotericin B

unequivocal to exclude or to establish a definitive diagnosis of IFI, as well as to indicate or discard the beginning of specific antifungal treatment.

Changes related to antifungal knowledge

The therapeutic armamentarium has not changed substantially in the last decade, which continues to include the three classical antifungal families: polyenes, azoles and echinocandins (figure 3).

Amphotericin is the antifungal agent with the broadest spectrum of activity, including both yeasts and the majority of filamentous fungi against which is a fungicidal drug[61,62]. The intrinsic resistance is against the most prevalent fungi is scarce[63] and secondary resistances, up to the present time, are very rare despite the fact that this compound has being used for over 50 years[64]. On the other hand, some observational studies have documented a low incidence of breakthrough IFI[65]. The incidence of infusion reactions and nephrotoxicity, the most frequent adverse events of amphotericin B, has been significantly reduced with lipid formulations and, in particular, with the liposomal formulation probably in relation to the higher stability of the liposome at the body temperature[66-68]. Liposomal amphotericin B is the formulation recommended by the majority of guidelines and experts opinion due to its tolerability and lower toxicity[12,13,69,70]. Liposomal amphotericin B is used at doses of 3 mg/kg/day for the treatment of *Aspergillus* infection[71] and 5-7 mg/kg/day in *Mucorales* infection[72]. The most appropriate dose for the use in prophylactic therapy is currently being assessed in an ongoing clinical trial[73].

EEA, voriconazole and posaconazole, are fungicides against filamentous fungi and have fungistatic activity against yeasts[62]. These drugs are currently the agents of choice for prophylaxis, and voriconazole together with liposomal amphotericin B are the best agents for the treatment of aspergillosis. Voriconazole has no activity against *Mucorales*. Conversely, posaconazole is active against some species *Mucorales*, (*Lichteimia, Rhizomucor*), however, amphotericin remains the treatment of choice in infections caused by these fungal speciesi[72,74]. The most remarkable disadvantages of the use of EEA in prophylactic regimens are as follows: a) potential interactions with other drugs (vincristine, cyclophosphamide, cyclosporine, sirolimus and drugs that cause QT prolongation) through modification of the activity of cytochromes[20-23] and, b) the probability of not reaching effective serum concentrations[75-77], with the associated risk of breakthrough infections[11,78-80]. This disadvantage is more noticeable in the case of posaconazole due to its limited oral absorption and large interindividual variability. The problem is further complicated if the patient is treated with antacids or proton pump inhibitions, or presents mucositis or diarrhoea. To solve this inconvenience it is advisable to increase the doses and to administer the drug with fat-rich meals[81-84]. Voriconazole has a more favourable bioavailability but currently it is recommended to reach serum concentrations > 1 mg/dL for which doses of 300 mg/12 h should be administered[85,86]. Hepatotoxicity, usually moderate and reversible, is the main adverse effect of azoles. Cases of photosensitivity and squamous cell carcinoma as a result of the prolonged use of voriconazole have been reported, although at present are anecdotic cases and the mechanism of action is unknown[87,88].

Echinocandins constitute a pharmacological group with excellent *in vitro* activity and efficacy against *Candida* spp., according to which the Infectious Diseases Society of America (IDSA)[14] and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[89] recommend echinocandins as the antifungals of

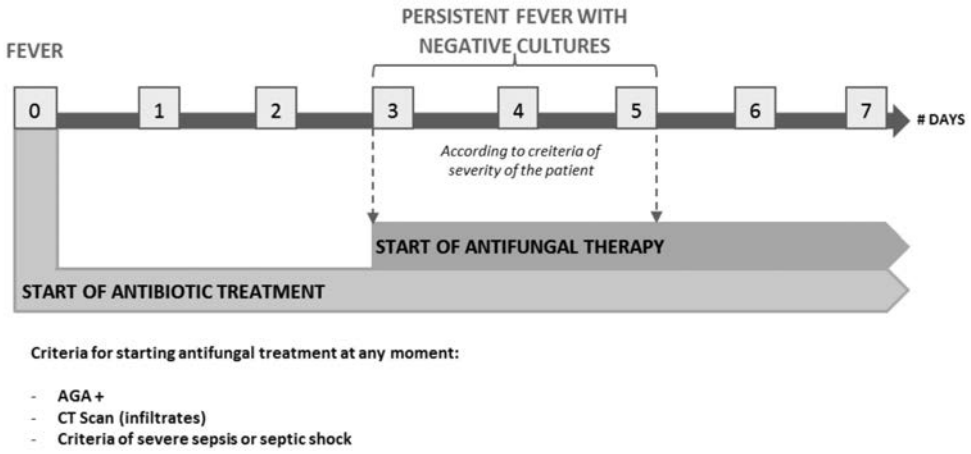


Figure 4 | **Time-out/starting antifungal treatment intervals in the high-risk patient**

choice for the treatment of candidemia and invasive candidiasis. However, the activity against the large majority of filamentous fungi is scarce. In the particular case of *Aspergillus* spp., the efficacy is not related to the *in vitro* activity probably due to its fungistatic effect[62]. In relation to caspofungin, two clinical studies of first-line treatment in onco-haematological patients with invasive aspergillosis have shown a lower efficacy than the target objective (relative risk [RR] > 35%)[5,90]. A further dose escalation study to assess the tolerability in haematological patients with 50% of possible IFIs[91], the 200 mg dose was more effective than 50 mg, although the results obtained were not superior to those reported with voriconazole in the study of Herbrecht et al.[92] in 2002, and with liposomal amphotericin B in the the AmBiLoad study of Cornely et al.[71] in 2007. Recently, different studies of caspofungin have shown the appearance of breakthrough fungemias caused by Aspergillus[6,65,93-95]. Micafungin is the only candin approved by the FDA for the prophylaxis of candidiasis in haematopoetic transplant recipients, although the dose required for the prophylaxis of infections caused by filamentous fungi may be higher than that recommended[96-99]. Finally, echinocandins have shown an excellent safety profile[100]. The efficacy of liposomal amphotericin B, echinocandins and voriconazole according to the clinical experience is shown in table 1[48,101].

ACCORDING TO THIS KNOWLEDGE, SHOULD WE CHANGE THE CURRENT TREATMENT STRATEGY IN THE HIGH-RISK PATIENT?

Prophylaxis

The indication of EEA as antifungal prophylaxis in high-risk patients is a highly recommendable strategy due to the high mortality associated with IFI. The possibility of oral administration makes these agents the antifungals of choice[8,14-19]. However, other alternatives such as micafungin or liposomal amphotericin B are necessary in some circumstances, including the following: 1) Concomitant treatment with vincristine, cyclophosphamide and sirolimus, or drugs that induce biosynthesis of cytochrome CYP3A4 or QT prolongation[20-23]; 2) severe liver failure[102]; and 3) absorption- or metabolism-related problems limiting the drug bioavailability[75-77,85].

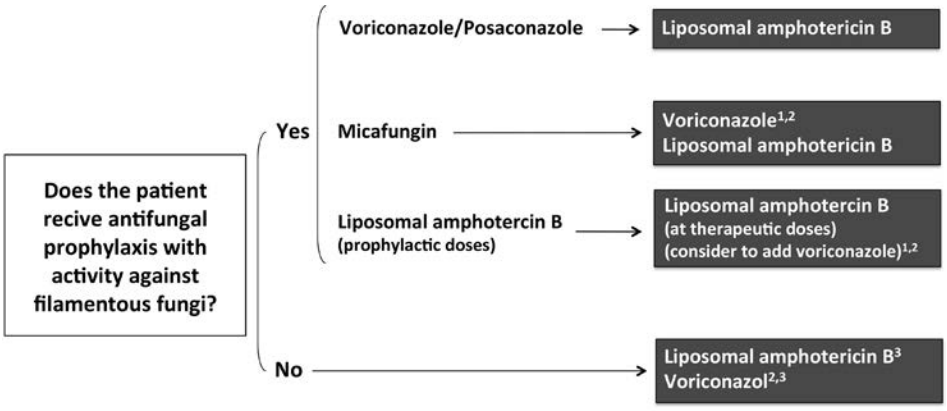
Preemptive treatment

The antifungal of choice for preemptive therapy, based on the positivity of the AGA test, is voriconazole. Liposomal amphotericin B is an option for cases in which voriconazole cannot be administered or appearance of adverse events that discourage its use. If the patient meets criteria of severe sepsis (signs of poor peripheral perfusion or functional failure of an organ), presents disseminated infection, involvement of the central nervous system (CNS) or radiological documentation of extensive respiratory involvement, then it is advisable to add a second antifungal drug in order to ensure the efficacy of treatment from the beginning. Approximately 20% of patients treated with voriconazole may have suboptimal serum concentrations during the first days of treatment[86,103].

Empirical treatment

Starting empirical treatment is considered adequate in case of persistence of fever and/or absence of clinical improvement despite antibiotic therapy, and negative microbiological studies. According to the risk level of fungal infection and clinical severity, treatment should be considered from the third day (high-risk patient and/or clinical worsening) or the fifth day (medium-risk and/or clinical stability)[13,49] (figure 4). The selection of the antifungal agent depends on whether the patient is being treated prophylactically and the antifungal drug used for prophylaxis.

If prophylaxis is being carried out with: 1) an EEA (posaconazole or voriconazole), liposomal amphotericin B is the treatment of choice; 2) in case of prophylaxis with micafungin, treatment with liposomal amphotericin B or voriconazole can be indica-



[1]If the patient was on prophylaxis with micafungin probably there is some contraindication for the use of triazoles.
[2]If the patient meets criteria of severe sepsis (signs of poor peripheral perfusion or functional failure of an organ), it is necessary that antifungal treatment should be effective as soon possible. Up to 20% of patients treated with voriconazole, optimal serum concentrations during the first week of treatment are not reached, so that initial treatment may include the association of voriconazole and liposomal amphotericin B or liposomal amphotericin B as monotherapy.
[3]If the AGA test is unavailable or negative, liposomal amphotericin B should be used. Caspofungin is an alternative option for cases in which the recommended regimens of choice cannot be used. Its activity and clinical efficacy against filamentous fungi are lower than those of triazoles and polyenes.

Figure 5 Selection of early antifungal treatment

ted. The antifungal drug should be selected taking into account the reasons for which the patient was treated prophylactically with micafungin instead of a triazole; and 3) in case of the patient given prophylactic treatment with low or intermittent doses of liposomal amphotericin B given intravenously or inhaled, treatment may include switching liposomal amphotericin to therapeutic doses in association (or not) to a second antifungal, voriconazole or a candin, although it is likely that some contraindication for the use of voriconazole may have been present if the patient was receiving triazole antifungals for prophylaxis.

Finally, if the patient was not treated with prophylactic antifungals and the AGA test is negative or unavailable, treatment with liposomal amphotericin B, voriconazole or caspofungin can be administered. However, when the antifungal agent is directed to treat a filamentous fungus, candin is considered the second choice drug following liposomal amphotericin and voriconazole (figure 5)[6,10, 65,93-95].

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