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Consensus subjects

Prophylaxis and treatment of fungal infections in oncohematological patients

Spanish Society of Chemotherapy and Spanish Society for Hematology and Hemotherapy

INTRODUCTION

The advances in the prevention and treatment of infections caused by bacteria and herpesviruses, combined with the use of hematopoietic growth factors and improvements in other support measures for neutropenic patients, have significantly increased the survival rate of patients treated with intensive chemotherapy and recipients of hematopoietic progenitors. This has allowed for:

- Increasing the number of people who benefit from these treatments (older patients and patients with a poorer general condition, and use of donors not fully compatible)

- Using more intensive chemotherapy or conditioning regimens (increased myeloablation or immunosuppression).

The increased extent and duration of cellular immunosupression, combined with a decreased mortality related to the procedure, have resulted in a gradual increase in the fungal infection rate in these patients. On the other hand, recently developed non-myeloablative conditioning regimens (1-3) decrease the duration of neutropenia and the severity of mucositis as compared to conventional schemes. The incidence of bacterial infections (4) and, probably, systemic infection by *Candida* spp. (4, 5) decrease during the first 30 days. By contrast, the risk of infection by *Aspergillus* spp. has remained at least the same as for transplants with myeloablative conditioning regimens (4).

Invasive fungal infections occur in 10% to 50% of patients with neutropenia or recipients of a transplant of hematopoietic progenitors, and are the leading infectious cause of death, with an attributable mortality close to 50%. *Candida* spp. and *Aspergillus* spp. rank first by order of frequency (6, 7), followed by other segmented hyaline fungi such as *Fusarium*, *Scedosporium* and *Paecilomyces*, dematiaceous fungi such as *Exophiala*, *Bipolaris* and *Alternaria*, non-septate fungi such as mucorales and yeast-like fungi, including *Trichosporon*, *Cryptococcus*, *Malassezia* and *Rhodotorula* species. The crude mortality rate of invasive fungal infection caused by *Aspergillus* spp. (68% to 95%) has not substantially changed over the past decade; by contrast, the death

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rate of invasive infection by *Candida* spp. (20% to 40%) has decreased since prophylaxis with fluconazole was introduced.

Three elements are essentially involved in the pathogenesis of fungal infection, as for any other type of infection: the size of the fungal inoculum, the degree of immunosuppression, and the pathogenicity or virulence of the fungus. Indeed, all risk factors for invasive fungal infection identified in different studies ultimately act by modifying one or more of these elements to a greater or lesser extent.

Invasive fungal infection by *Candida* spp. usually occurs from yeasts that colonize the skin and mucosal membranes (endogenous infection). The extent of the colonized surface and the density of *Candida* population, on the one hand, and the loss of mucosal integrity, on the other hand, are determinant factors of the size of the fungal inoculum. The use of broad spectrum antibiotics (8, 9), the number of antibiotics administered, treatment duration, bacteremia episodes (9-11), parenteral nutrition, and corticosteroid therapy (12) have been identified as risk factors for *Candida* infection. By different mechanisms, all these factors promote colonization of mucosal membranes by *Candida*; moreover, bacteremia may be a marker of mucositis (or of an increased permeability of the mucosal membranes), and parenteral nutrition is associated to a certain degree of atrophy in the intestinal mucosa.

Neutropenia severity (<100/µl) and duration (more than 7 days) define the impairment of the defense mechanisms against invasive infection by *Candida* spp. The underlying disease, the conditioning regimen (9, 13, 14) and the degree of compatibility of the graft are determinant factors of the severity of neutropenia. Thus, acute leukemia (15), administration of high doses of cytosine arabinoside, and graft-versus-host disease result in an increased severity and duration of neutropenia, and also in an increased severity of mucositis.

Fungal virulence factors are less well known and do not appear to have a significant impact in the development of most cases of invasive fungal infections. However, mucosal colonization by *Candida tropicalis* has been seen to be highly predictive for invasive infection by this species (16, 17).

In infections caused by *Aspergillus* or other filamentous fungi, contagion usually occurs through spore inhalation (exogenous infection). The size of the inoculum depends on the density of spores present in the air. Infection is less common if the patient is hospitalized in a room with high efficiency air filters (18). Neutropenia and deficient activity of alveolar macrophages due to corticosteroid therapy, graft-versus-host disease, or the use of a graft with a reduced T lymphocyte content are risk factors for invasive *Aspergillus* infection (19-21).

This article is the result of several meetings held during 2002 among members of the Spanish Society of Chemotherapy (SEQ) and the Spanish Society for Hematology Hemotherapy (AEHH), in which guidelines for prophylaxis, empirical treatment and specific treatment for infections caused by *Candida* spp. and *Aspergillus* spp. in oncohematological patients, particularly recipients of transplants of hematopoietic progenitors, were reviewed, and a consensus was reached. Some of the recommendations in this document are not included in the prescribing information for the new antifungals (caspofungin and voriconazole). However, in the opinion of the authors, the use of these antifungals is warranted by the recently reported clinical experience, the high mortality of some conditions despite treatment with amphotericin B, and the potential toxicity of the currently available alternatives.

The document uses the term “lipid formulations” to designate both the lipid complex and the liposomal formulation of amphotericin B when their efficacy or indications are considered to be equivalent. The formulation or dosages are only specified in particular

situations where differences may exist between them. Lipid preparations of amphotericin B administered at doses of 3-5 mg/kg/day have a similar efficacy to doses of 0.6-1 mg/kg/day of amphotericin B deoxycholate, but are less nephrotoxic, and the side effects related to administration are also less common. The results of a recently reported study (22) suggest that the tolerability of amphotericin B deoxycholate is improved and its nephrotoxicity is reduced, with no loss of clinical efficacy, if the drug is administered as a continuous (24-hour) infusion rather than over shorter periods (4 hours).

The clinical experience reported suggests that voriconazole probably has a superior clinical efficacy to amphotericin B deoxycholate for the treatment of invasive infections caused by *Aspergillus* spp. (23), and that caspofungin has a superior efficacy in invasive infections caused by *Candida* spp. (24). Table 1 shows the conditions that justify the choice of an alternative treatment to amphotericin B deoxycholate in an invasive fungal infection. These essentially include conditions in which there is a certain degree of renal failure or a significant risk of developing renal failure during the treatment. It is also advisable to consider the selection of an alternative less nephrotoxic or better tolerated antifungal (caspofungin, voriconazole, or a lipid formulation of amphotericin B) in conditions requiring long-term use of high doses of amphotericin B deoxycholate (≥1 mg/kg/day), and when empirical treatment is started under circumstances in which the probability that the patient experiences an invasive fungal infection is lower than the risk of the occurrence of severe toxicity associated to the use of amphotericin B deoxycholate.

Table 2 includes the doses and administration routes of the main antifungals used to treat invasive fungal infections in adult patients.

Table 1. Conditions justifying the choice of an alternative treatment[1] to amphotericin B deoxycholate in invasive infections by *Candida* spp. or *Aspergillus* spp.
- Serum creatinine ≥1.8 mg/dl, doubling of the initial value during treatment, or creatinine clearance <50 ml/min.
- Need for using other drugs that may be nephrotoxic (cyclosporin[2], cisplatin, tacrolimus).
- Occurrence of infusion-related adverse effects that do not improve with symptomatic treatment
- Patient in a shock state[3].

[1]Caspofungin, voriconazole (in the event of renal failure with glomerular filtration rate <50 ml/min, the IV formulation should not be used), or a lipid formulation of amphotericin B.
[2]Patients treated with cyclosporin may develop renal failure if they receive amphotericin B, even in low doses. Cyclosporin dosage should be decreased by at least 50% if voriconazole is administered.
[3]In a hypoperfusion status associated to severe sepsis, both the development of renal failure and its consequences are frequent and particularly serious.

INDICATIONS AND GUIDELINES FOR ANTIFUNGAL PROPHYLAXIS IN NEUTROPENIC PATIENTS (Tables 3 and 4)

Studies on antifungal prophylaxis performed during neutropenia periods, particularly those associated to hematopoietic progenitor transplant, have shown that:

- Amphotericin B used at low doses (0.1-0.2 mg/kg/day IV) or on alternate days does not decrease the incidence of systemic fungal infection (25). Indeed, it is unlikely that the serum levels achieved may prevent infection by *Aspergillus* spp. (26). The need for intravenous administration, the infusion-related side effects, and the potential nephrotoxicity when it is administered together with cyclosporine limit its

use. Administration in nebulized form has been effective for reducing the incidence of aspergillosis in lung transplant recipients (27, 28); however, the benefits in neutropenic patients have been marginal (29) or not proven (30). Moreover, its use may be impaired by the occurrence of side effects (bronchospasm, nausea, vomiting).

- While both oral ketoconazole (31, 32) and intravenous miconazole (33) appear to be effective for the prevention of fungal infection, the variable oral bioavailability of the former (particularly in relation to mucositis in patients receiving a hematopoietic progenitor transplant), the need for intravenous administration of the former, and the higher toxicity of both as compared to fluconazole have markedly limited their use.

Table 2. Doses and administration routes of the main drugs used for treating invasive fungal infections in adult patients.	
Amphotericin B deoxycholate	0.3-1.5 mg/kg/24 h IV[1.]
Amphotericin B lipid complex	3-5 mg/kg/24 h IV
Liposomal amphotericin B	1-5 mg/kg/24 h IV[2]
Caspofungin	Initial loading dose (1st day) 70 mg IV, followed by 50 mg/24 h IV[3]
Fluconazole	Initial loading dose (1st day) 300-400 mg/12 h p.o. or IV, followed by 200 mg/12 h p.o. or IV
Itraconazole	Initial loading dose (2 days) 200 mg/12 h IV, followed by 200 mg/24 h IV[4], or an initial loading dose (3 days) of 200 mg/8 h as oral solution followed by 200 mg/12 h as oral solution
Voriconazole	Initial loading dose (1st day) 6 mg/kg/12 h IV, followed by 4 mg/kg/12 h IV, or an initial loading dose (1st day) of 400 mg/12 h p.o. followed by 200 mg/12 h p.o.

[1]0.3-0.6 mg/kg/24 h in esophageal candidiasis, 0.7-1 mg/kg/24 h for candidemia, 1-1.5 mg/kg/24 h in invasive aspergillosis. Doses higher than 50 mg/day do not increase plasma levels, but may be more effective for treating invasive infection by *Aspergillus*.
[2]Doses up to 10 mg/kg are tolerated with no increase in nephrotoxicity. From 10 mg/kg, serum levels remain stable.
[3]In patients over 80 kg of weight, consider administration of 70 mg/day IV
[4]When available.

Table 3. Risk criteria for infection by *Candida* spp. during an episode of neutropenia. Indications and guidelines for prophylaxis.	
Major criteria	Minor criteria
- Isolation of *Candida* spp. from two or more mucosal membranes	- Isolation of *Candida* spp. from a mucosal membrane
- Isolation of *C. tropicalis* from a mucosal membrane	- Broad spectrum antibiotic therapy for at least one week
- Candiduria	- Corticosteroid therapy (≥20 mg/day of prednisone)
- History of chronic hepatosplenic candidiasis	- Parenteral nutrition - Significant mucositis (grade ≥2)
Indication for prophylaxis: the risk of systemic infection by *Candida* spp. is high in the neutropenic patient who meets one major criterion or two minor criteria. In this situation, prescription of prophylaxis should be considered, particularly if the neutropenia is expected to last longer than 10 days.	
Guidelines for prophylaxis: fluconazole, 200 mg/12-24 hours by the oral route until neutropenia resolves. In patients undergoing an allogenic transplant of hematopoietic progenitors, maintenance of fluconazole for 2-3 months after the procedure appears to be beneficial.	

Table 4. Risk criteria for *Aspergillus* infection and indications for prophylaxis in oncohematological patients.	
Presence of two of the three following criteria: - Neutropenia (<100/μl)) expected to last longer than two weeks - Long-term[1] corticosteroid therapy (≥20 mg/day of prednisone) - Acute (grade ≥2) or chronic extensive graft-versus-host disease + - Patient staying in a room with no filtered air (HEPA or similar)	Consider starting primary prophylaxis[2] with itraconazole oral solution[3]
- New episode of neutropenia in a patient with a history of apparently cured aspergillosis	Secondary prophylaxis with itraconazole oral solution[3]
- Detection of galactomannan antigen[4] or *Aspergillus* DNA by PCR[4] in a patient asymptomatic or with fever for no apparent reason	"Pre-emptive" treatment with voriconazole

[1]Current or expected long-term treatment (longer than two weeks).

[2]Particularly if other cases have been seen at the unit or construction work is underway at the hospital or its surroundings.

[3]Alternatively, voriconazole or other regimen suggested for the treatment of aspergillosis may be used (see Table 8). An alternative to itraconazole is advisable if itraconazole serum levels cannot be measured and the existence of mucositis poses doubts about absorption.

[4]At least two consecutive positive measurements.

- Oral fluconazole at a dose of 400 mg/day during the neutropenia period of the transplant of hematopoietic progenitors significantly decreases the incidence of both superficial and invasive fungal infection, infection-related mortality, and the need for starting empirical antifungal treatment (34, 35). Lower doses (100-200 mg/day) also appear to be effective (36), but the evidence is less. In a revision of 355 necropsies from patients who died in the months following a hematopoietic progenitor transplant, a significantly lower incidence of liver infection by *Candida* spp. was seen in patients given prophylaxis with fluconazole (37). In patients with acute leukemia and neutropenia secondary to chemotherapy, prophylaxis with fluconazole 400 mg/day significantly decreased the extent of colonization and the rate of documented fungal infections, particularly superficial infections (38). Some authors have reported an increase in infections caused by *Candida krusei* and *Candida glabrata* (39, 40) associated to the use of fluconazole. *Candida krusei* is intrinsically resistant to fluconazole, and *Candida glabrata* rapidly acquires resistance by mutant selection during treatment; however, studies comparing prophylaxis with fluconazole versus placebo (35, 38) have seen no significant differences in the incidence of candidemia by *C. krusei*, despite the fact that the prevalence of fecal colonization by this species was higher in patients receiving fluconazole. In a study (41), a selective increase in fecal colonization by *Candida* spp. was seen in patients receiving fluconazole as compared to the group treated with oral polyenes. This probably reflects the low fecal levels of fluconazole, due to

its high bioavailability, and warrants the recommendation by some authors (42) to associate fluconazole with oral administration of amphotericin B. Very few cases of resistance development in *Candida albicans* have been reported in patients receiving a hematopoietic progenitor transplant on fluconazole prophylaxis (43), as opposed to AIDS patients treated for similar periods of time (44). The results of a meta-analysis of 16 randomized studies comparing the prophylactic efficacy of fluconazole to oral administration of polyenes or placebo in neutropenic patients show that administration of fluconazole 400 mg/day significantly reduces the incidence of invasive fungal infection in recipients of a hematopoietic progenitor transplant (45). In this situation, the incidence of systemic fungal infection in patients not receiving prophylaxis is higher than 15%. By contrast, in neutropenia not associated to transplantation of hematopoietic progenitors, in which the expected rate of invasive infection is under 15%, fluconazole administration showed no significant influence on the frequency of deep infection, and only significantly decreased the incidence of superficial fungal infection. The impact on superficial infection was seen even when doses of 50-200 mg/day were used. Though patients receiving fluconazole prophylaxis showed an increased frequency of colonization by fungi resistant to this antifungal drug (*C. krusei* and *C. glabrata*), this was not associated to an increase in the number of systemic infections. As regards duration of the prophylaxis, in a placebo-controlled study (46) conducted on patients undergoing allogenic transplantation of hematopoietic progenitors, administration of fluconazole 400 mg/day for 75 days after the transplant decreased the incidence of invasive candidiasis and the associated mortality in both the early and late periods. The incidence of graft-versus-host disease with intestinal involvement was also lower in patients who received fluconazole. After eight years of follow-up, the survival rate was significantly greater in the group given fluconazole.

- A significant limitation of fluconazole prophylaxis is its low or nil activity against most filamentous fungi of clinical interest, including the different *Aspergillus* species. Itraconazole is active against *Aspergillus* spp., and its new oral formulation with cyclodextrin can achieve effective serum levels against such species. In a study comparing prophylaxis with itraconazole, administered at doses of 100 mg/12 hours, to the association of amphotericin B with nystatin in neutropenic patients (47), no significant differences were seen in the incidence of fungal infections; however, in two studies comparing itraconazole to fluconazole, in which itraconazole was used at doses of 200 mg/12 hours, superior results to those of fluconazole were obtained, with a significantly lower incidence of episodes of *Aspergillus* infection in the itraconazole arm (48, 49). However, due to the irregular intestinal absorption of itraconazole, its poorer oral tolerability, the higher risk of interference with the metabolism of other drugs as compared to fluconazole, and the low incidence of infection by *Aspergillus* spp. in patients admitted to rooms with filtered air, the selection of itraconazole for prophylaxis regimens should be reserved for the specific situations of risk of infection by *Aspergillus* spp. discussed below.
- The factors that have been associated to the development of systemic infection by *Candida* spp. in neutropenic patients may be classified according to their importance in major and minor risk criteria (Table 3). The former include isolation of *Candida* spp. from two or more mucosal membranes (50, 51), isolation of *C. tropicalis* from one mucosal membrane (17), the existence of candiduria, and a history of an episode of chronic hepatosplenic candidiasis (52, 53). The risk associated to each of these individual factors is sufficiently high as to warrant the start of a prophylactic

regimen. Minor criteria include the finding of *Candida* spp. in the same site in two consecutive cultures, and several situations that are associated to a high probability of mucosal colonization or invasion by *Candida* spp., such as having received broad spectrum antibiotic therapy for over one week, treatment with corticosteroids at doses of 20 mg/day or higher, parenteral nutrition, and grade ≥2 mucositis.

- The risk factors for *Aspergillus* infection include long-term neutropenia, severe (grade ≥2) or chronic extensive graft-versus-host disease (54), and treatment with corticosteroid doses higher than 20 mg/day of prednisone. In any of these situations, the risk is high when the patient is not hospitalized in a room with filtered air, particularly if cases of *Aspergillus* infection have been seen in the hospitalization area or construction work is underway at the hospital or the surrounding area. A history of prior aspergillosis is a risk factor for reactivation after new chemotherapy courses (55). Exacerbations associated to new episodes of immunosuppression have been seen, even in patients in whom infection appeared to be controlled. Antifungal treatment can prevent recurrence in most of these cases (55, 56).

Based on the experience discussed above, it is considered that an indication exists to start prophylaxis for *Candida* spp. in patients with neutropenia associated to allogenic transplantation of hematopoietic progenitors and in any other situation of neutropenia when the patient meets at least one major risk criterion or two minor risk criteria for invasive infection (Table 3). The indication is particularly warranted if it is expected that the episode of neutropenia could last longer than 10 days. The antifungal of choice is fluconazole, administered by the oral route at doses of 200 mg/12-24 hours until recovery from neutropenia occurs. In patients undergoing allogenic transplantation of hematopoietic progenitors, it is advisable to maintain prophylaxis until two or three months after the transplant.

Indications for prophylaxis against *Aspergillus* are not so well defined. Table 4 describes the conditions in which it is indicated or recommended. Both primary and secondary prophylaxis may be performed with itraconazole oral solution. While no sufficient experience is available with voriconazole or other parenterally administered antifungals, their use may be considered if the oral route cannot be used for any reason or itraconazole is not considered appropriate (57).

GUIDELINES FOR EMPIRICAL ANTIFUNGAL TREATMENT IN NEUTROPENIC PATIENTS WITH PERSISTENT FEVER DESPITE ANTIBIOTIC TREATMENT

An indeterminate number of patients with neutropenia and fever not responding to antibiotic treatment have a fungal infection (58). In the eighties, the results of a study by Pizzo (59) and a subsequent study of the EORTC (60) provided data supporting the potential benefit of starting an empirical antifungal treatment when neutropenic patients continued to show fever after four to six days of antibacterial treatment. Patients included in these studies had not been given antifungal prophylaxis with any of the currently recommended regimens (fluconazole or other systemic azoles). On the other hand, the statistical power of both studies is limited due to the low number of episodes analyzed.

Studies comparing the clinical efficacy of amphotericin B deoxycholate to that of different lipid formulations of amphotericin (61, 62), fluconazole (in patients not receiving it as a prophylaxis regimen) (63, 64), or itraconazole (65), as well as studies comparing liposomal amphotericin B to the lipid complex (66) or to voriconazole (67), have seen no significant differences in the number of patients achieving defervescence

in each of the therapeutic arms. However, some of these studies have found a reduction of the number of episodes of breakthrough fungemia (61), and a better tolerability profile of the alternative antifungal as compared to amphotericin B deoxycholate has been seen in most of them (61-65). An analysis of the clinical significance of the nephrotoxicity associate to the use of amphotericin B has clearly demonstrated the relationship of this complication with a higher mortality rate and a significant prolongation of hospital stay (68).

Based on the result of the different studies on empirical antifungal treatment, the possibility that persistent fever in neutropenic patients is due to a fungal infection is low (probably under 10%) if the patient is receiving prophylaxis with fluconazole and is hospitalized in a room with effective environmental isolation measures. In this situation of low risk of fungal infection, it is particularly important that the antifungal empirically administered is well tolerated, has a low toxicity, and does not interfere with the rest of the medication received by these patients.

Lipid formulations of amphotericin B are substantially less nephrotoxic than amphotericin B deoxycholate; however, renal toxicity (defined by a doubling of serum creatinine levels) is still over 10% in the best of cases (liposomal amphotericin B) (61), and is particularly high in recipients of an allogenic transplant of hematopoietic progenitors (69). The toxicity and side effects of voriconazole, and particularly caspofungin, are lower than those of amphotericin B in any of its formulations.

The choice of the appropriate antifungal should be decided based on the risk of infection by a *Candida* species resistant to fluconazole or by *Aspergillus* spp. (Table 5):

- If the patient is hospitalized in a room with filtered air and is not receiving prophylaxis with an azole, there is not significant risk of inhalation of *Aspergillus* spp. spores or infection by *Candida* species resistant to fluconazole. In this situation, empirical antifungal treatment may be started with fluconazole, administered preferably by the intravenous route. As an alternative, amphotericin B deoxycholate may be administered at doses of 0.6 mg/kg/day by the intravenous route.

- In the event that the patient is receiving prophylaxis with an azole or is hospitalized in a room with no high-efficiency filters, there is a risk in the first situation of infection by *Candida* species with a decreased susceptibility or resistant to fluconazole (*C. glabrata* and *C. krusei*, respectively), while in the second case there is a risk of inhalation of *Aspergillus* or other filamentous fungi. In both cases, empirical antifungal treatment may be started with high doses (0.7-1 mg/kg/day) of amphotericin B deoxycholate, in an attempt to reach serum levels effective against *Aspergillus* and less susceptible *Candida* species (*C. glabrata* and *C. krusei*) (70). However, under these circumstances and for the reasons discussed above, it would be preferable to select the least toxic and better tolerated antifungal, such as caspofungin or liposomal amphotericin B. If the existence of a fungal infection is no confirmed, treatment is maintained until the resolution of neutropenia (neutrophil count >1000/µl).

The experience obtained in children with cancer and neutropenia using a test for genetic detection of *Aspergillus* using PCR has been recently reported (71). Fungal DNA was detected more than once in 31 of 83 episodes of fever, and antifungal treatment was started. In 26 of these 31 episodes (84%), the existence of a fungal infection was subsequently shown. If the sensitivity of rapid diagnostic tests is confirmed (72), a positive result will not only allow for starting antifungal treatment earlier, but also for substantially reducing the number of patients treated on an empirical basis.

Table 5. Indications and guidelines for empirical antifungal treatment recommended in neutropenic patients with persistent fever.	
- Patient not receiving prophylaxis with an azole and admitted to a room with filtered air (HEPA or similar)[1]: From the fourth to the sixth day of persistent fever for no apparent cause, the start of empirical antifungal treatment is indicated. Fluconazole can be used. As an alternative, amphotericin B deoxycholate may be used at a dose of 0.6 mg/kg/day. - Patient on prophylaxis with an azole[2] or hospitalized in a room with no laminar air flow or HEPA filers[3]: From the fourth to the sixth day of persistent fever for no apparent cause, the start of empirical antifungal treatment is indicated. Amphotericin B deoxycholate can be used at a dose of 0.7-1 mg/kg/day, or preferably a less toxic and better tolerated antifungal, such as caspofungin or a lipid formulation of amphotericin B, or itraconazole IV when available.	If the existence of a fungal infection is not confirmed, treatment is maintained until recovery from neutropenia

[1]In this situation, the risk of inhalation of *Aspergillus* spp. or infection by *Candida* species resistant to fluconazole is very low.

[2]These patients are at risk for infection by *Candida* species with a decreased susceptibility (*C. glabrata*) or resistant (*C. krusei*) to fluconazole.

[3]In this situation, there is a risk of inhalation of *Aspergillus* or other filamentous fungi.

TREATMENT GUIDELINES FOR OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS IN NEUTROPENIC PATIENTS

Oropharyngeal and esophageal candidiasis is caused in most cases by *C. albicans*. Pharyngeal, but not esophageal, involvement can be treated with a topical azole (clotrimazole) or nystatin mouthwashes for one to two weeks; however, in neutropenic patients fluconazole and itraconazole should preferably be used in both forms (oropharyngeal and esophageal). Treatment is continued for one to two weeks in oropharyngeal infection, and for two to three weeks in esophageal infection. If the patient has swallowing difficulties, fluconazole can be administered at the same dose by the intravenous route. Infections occurring while the patient is receiving fluconazole prophylaxis, as well as infections not responding or relapsing early after the use of an azole, can be treated with amphotericin B deoxycholate at a dose of 0.3-0.6 mg/kg/day or the equivalent doses of a lipid formulation, caspofungin or voriconazole (oral or intravenous). The results of three randomized, double-blind studies comparing caspofungin to amphotericin B deoxycholate for the treatment of esophageal candidiasis (73), or esophageal and oropharyngeal candidiasis (74), and to fluconazole in esophageal candidiasis (75) in AIDS patients have been reported. While both the clinical and microbiological cure rates were higher in the group treated with caspofungin than in the amphotericin B group, the difference was not statistically significant. However, side effects were markedly less common in patients receiving caspofungin. Voriconazole has been compared to fluconazole in a double-blind study (76) including patients with AIDS and esophageal candidiasis. Clinical efficacy was similar, but there was a higher incidence of adverse effects in the voriconazole arm. Both caspofungin and voriconazole have been effective for treating cases of esophagitis caused by *C. albicans* strains resistant to fluconazole in AIDS patients (77, 78).

TREATMENT GUIDELINES FOR CHRONIC DISSEMINATED CANDIDIASIS OR HEPATOSPLENIC CANDIDIASIS

In chronic disseminated candidiasis, therapeutic success probably depends more on the long-term use of an antifungal active against the species involved than on the drug itself. Several observational studies have shown that fluconazole has an efficacy of 80% or higher both as primary treatment (79) and as rescue treatment after conventional amphotericin B has failed (80, 81), whereas the efficacy of amphotericin B ranges from 50% to 65% (82, 83). Lipid formulations of amphotericin reach liver and spleen levels significantly higher than the conventional preparation (84), but the potential clinical benefit of this has not been shown; however, preliminary evidence suggests that lipid formulations are effective even in patients in whom the conventional preparation has failed (85, 86). There is still little experience with caspofungin and voriconazole.

In patients who have not received prophylaxis with fluconazole and have no history of fungemia or colonization by *Candida* resistant to fluconazole, and in patients in whom infection by a susceptible species is documented, the treatment of choice is fluconazole at a dose of 300-400 mg/12 hours, initially administered by the intravenous route until clinical stabilization occurs (disappearance of fever and clinical improvement, together with evidence of stability in the size and number of focal lesions) and then by the oral route. In patients in whom infection by a resistant species is documented, or who are receiving fluconazole prophylaxis, conventional amphotericin B (0.7 mg/kg/day) or equivalent doses of a lipid formulation may be used.

Administration of oral voriconazole may be considered after clinical stabilization. Changes in lesions over time should be monitored by regular abdominal computed tomography, and treatment must be continued until lesions disappear or are calcified. Two to three months are usually required to see a radiographic response, and an average of six months until cure is obtained. The prognosis of patients with chronic disseminated candidiasis essentially depends on the course of the underlying disease, and the therapeutic plan for this should therefore be changed as little as possible. In patients in whom antifungal treatment has achieved clinical stabilization, the risk that focal lesions worsen or dissemination of candidiasis occurs during successive course of myeloablative chemotherapy, including those associated to hematopoietic progenitor transplantation, is minimal and does not warrant the delay in the application of appropriate measures for treating the underlying disease (52, 53), provided antifungal treatment is maintained.

GUIDELINES FOR ANTIFUNGAL TREATMENT IN NEUTROPENIC PATIENTS WITH *CANDIDA* ISOLATION FROM BLOOD CULTURES

The presence of neutropenia is associated to an increased mortality of candidemia episodes (87). In neutropenic patients, isolation of yeasts or *Candida* from one or more blood cultures should always be considered an indication for immediately starting an antifungal treatment. The drug of choice will depend on the *Candida* species isolated and on the clinical severity of infection. *C. albicans* may be identified in a relatively simple and rapid way using the germ tube test. If this information is not available, the possibility that the isolated species is resistant to fluconazole should be assessed. If the patient has received an azole for longer than seven days within the last month, or a *Candida* species resistant (*C. krusei*) or potentially resistant (*C. glabrata*) to fluconazole has been isolated from a prior culture of feces, urine, or a mucosal smear, it should be considered that a significant risk exists that the candidemia is caused by a species resistant to this antifungal.

In randomized studies conducted in patients without neutropenia, fluconazole has shown a clinical efficacy similar to amphotericin B deoxycholate (88, 89) in the treatment of candidemia. In neutropenic patients, several observational studies (84, 90) similar clinical success rates were obtained with fluconazole and conventional amphotericin B. No studies comparing conventional amphotericin B to the different lipid formulations in the treatment of candidemia have been reported. Caspofungin has been shown to be superior to amphotericin B deoxycholate in a randomized study where most of the patients (90%) had no neutropenia (24). Due to the apparent equivalent efficacy of currently available antifungals, the choice should be based on the susceptibility of the *Candida* species isolated, on the toxicity of the drug and, finally, on the cost of treatment.

Neutropenic patients with candidemia can be classified in two therapeutic groups based on their clinical status and the risk of infection by a *Candida* species resistant to fluconazole (Table 6):

1) The first group includes patients with primary or metastasic infection of an organ, patients who meet criteria for severe sepsis defined as hypotension, signs of skin hypoperfusion, or biological or clinical signs of dysfunction of an organ, and patients with risk factors for infection by a fluconazole-resistant *Candida* species. In any of these circumstances, treatment may be started with caspofungin, voriconazole or high doses of amphotericin B deoxycholate (0.7-1 mg/kg/day) or its equivalent of a lipid formulation, in order to treat a potential infection by poorly susceptible *Candida* species or by *C. tropicalis*. Infection by *C. tropicalis* appears to respond better to high doses of amphotericin B (1 mg/kg/day) (91). In the event of renal failure or septic shock, it is advisable to give priority to caspofungin or a lipid formulation of amphotericin B. Occasionally, if the course is unfavorable or the seriousness of the case justifies it, association of caspofungin with any of the two other antifungals (voriconazole or amphotericin B) can be considered.

2) The second group includes patients who do not meet any of the above criteria, in which case treatment can be started with fluconazole by the oral or intravenous route, depending on severity.

Liposomal amphotericin B reaches higher levels in brain parenchyma than the conventional formulation and all other lipid preparations (92). While there is no evidence of a greater clinical efficacy, this formulation, administered at high doses alone or combined with flucytosine (100 mg/kg/day), should be preferably used foe meningitis. Voriconazole can also be used.

Once the *Candida* species has been identified, treatment can be adapted based on its susceptibility pattern and on the evolution with initial treatment. For *C. albicans*, *C. tropicalis* or *C. parapsilosis* infections, if the course is favorable and there is no clinical evidence of visceral involvement, treatment can be continued with fluconazole at the previously recommended doses. *Candida lusitaniae* is less susceptible to amphotericin B and should be treated with fluconazole, voriconazole or caspofungin. Infection by *C. krusei* or *C. glabrata*, as well as severe infection or infection with visceral involvement by *C. albicans* or *C. tropicalis*, should be treated with caspofungin, voriconazole or high doses of amphotericin B as deoxycholate or in a lipid formulation.

Table 6. Guidelines for antifungal treatment in the event of isolation of *Candida*[1] from blood cultures.	
- Patient with primary or metastasic infection of an organ, with criteria for severe sepsis, or with risk factors for infection by *Candida* species resistant to fluconazole[2]: Treatment with caspofungin, voriconazole, amphotericin B deoxycholate 0.7-1 mg/kg/day or an equivalent dose of a lipid formulation. - Patient with none of the above criteria: Treatment with oral or IV fluconazole depending on severity	Once the *Candida* species is identified, continue following the recommendations specified in the text. Antifungal treatment must be maintained for up to two weeks after the last positive blood culture and until clinical signs and neutropenia are resolved[3].

[1] *Candida* not identified yet.

[2]Patient who has received prophylaxis with an azole for more than seven days in the last month or has a history of colonization of any mucosal membrane by *C. glabrata* or *C. krusei*.

[3]If evidence exists of an organ infection, the relapse rate is high and treatment must be continued from one to several months.

Antifungal treatment for an episode of candidemia must be maintained until clinical signs and neutropenia are resolved, and for at least two full weeks after the last positive blood culture. Necropsy studies from patients died after transplantation of hematopoietic progenitors have documented a high incidence of disseminated fungal infection with metastasic involvement of one or several organs (37). If visceral involvement occurs, the relapse rate is high, and treatment must be continued for one or several months, depending on the site. During the three months following the initial episode, the course should be monitored and a high suspicion index should be maintained if fever recurs.

MANAGEMENT OF THE CENTRAL VENOUS CATHETER IN NEUTROPENIC PATIENTS WITH CANDIDEMIA

Candidemia in a neutropenic patient is often the result of passage of yeasts through the intestinal or esophageal mucosa (8), particularly when neutropenia coexists with a significant mucositis. The catheter may either be colonized during the episode of candidemia or be the portal of entry of candidemia, particularly in patients on parenteral nutrition. A catheter colonized or infected by *Candida* must be removed, since the risk of metastasic dissemination or persistent candidemia is high despite treatment (93). However, since the source of candidemia is usually unknown, the catheter is frequently not colonized and its change may be complex, catheter removal is only recommended (94) in the following circumstances (Table 7):

Table 7. Indications for removal of a central venous catheter[1] in the event of candidemia.
- Isolation of *C. parapsilosis*.
- Phlebitis, cellulitis or signs of infection at the catheter insertion site.
- Criteria for severe sepsis or septic shock.
- Persistent or recurrent candidemia[2] or lack of clinical response after 72 hours of treatment with appropriate doses of an antifungal considered to be active[3].
- Risk factors for the development of infectious endocarditis.

[1]Provided the catheter cannot be done away with or replaced by a peripheral catheter.

[2]Positive blood cultures performed on different days. Two or more positive blood cultures from samples obtained with an interval longer than an hour probably suggest that the source of fungemia is the vascular catheter.

[3]Particularly if the catheter has been sealed with amphotericin.

- When the use of a central catheter is not indispensable or it is considered that a peripheral catheter may be appropriate.
- If candidemia is caused by *C. parapsilosis*, since the possibility that the catheter is the source of a fungemia by this yeast is significantly greater than for other *Candida* species (90).
- When phlebitis, cellulitis or signs of infection are seen in the catheter entry.
- If the patient shows criteria for severe sepsis or septic shock. The recommendation of catheter removal in this situation stems from the potential severity of the condition if the catheter was the source of fungemia.
- In the event of persistent or recurrent candidemia or lack of clinical response after 72 hours of treatment with appropriate doses of an antifungal considered to be active. In a review of 106 episodes of candidemia (94), it was noted that all patients with sustained fungemia, defined by the presence of positive blood cultures for longer than two days, had a central venous catheter inserted.
- If risk factors for infectious endocarditis exist, such as a prosthetic valve, history of a prior episode of endocarditis, or complex cyanotic congenital heart disease.

GUIDELINES FOR ANTIFUNGAL TREATMENT OF INVASIVE ASPERGILLOSIS (Table 8)

Approximately 80% of patients undergoing transplantation of hematopoietic progenitors who develop *Aspergillus* infection die despite treatment. Mortality is even greater when the infection involves certain organs, particularly the central nervous system (95-97). In addition, the development of respiratory failure represents an independent factor of poor prognosis in patients with fungal pneumonia (98, 99). Among antifungals that may be considered active (conventional amphotericin B, lipid formulations of amphotericin B, caspofungin, voriconazole, and itraconazole), only voriconazole and a lipid formulation of amphotericin B as a colloidal dispersion (not marketed in Spain) have been directly compared to conventional amphotericin B for the treatment of invasive aspergillosis. In an open-label, randomized study (23), a higher rate of favorable responses and a lower mortality were seen with voriconazole as compared to amphotericin B (53% versus 32% and 71% versus 58%, respectively), while in a double-blind trial (100) amphotericin B colloidal dispersion showed an

efficacy similar to the conventional formulation. Although a direct comparison of the different observations is inappropriate, a rough estimate of the relative efficacy of the other drugs can be obtained from non-comparative studies, in which these drugs were used to treat patients most of whom had experienced toxicity with amphotericin B deoxycholate. Under these circumstances, the efficacy (complete or partial response) of amphotericin B lipid complex has been estimated (101) at 42%, while liposomal amphotericin has been effective (84, 102) in approximately 60% of cases, and oral or intravenous itraconazole (103-105) in approximately 50% (in patients with hemopathies). The efficacy of caspofungin (106) has been 45% in patients who were in most cases (85%), refractory to treatment with other antifungals (different formulations of amphotericin B). In a study (107) using liposomal amphotericin B as primary treatment for invasive aspergillosis in neutropenic patients with cancer, the mean rate of favorable response was 55%. Although no data are available that allow for establishing whether or not differences exist in the efficacy of the different amphotericin B preparations, some observations suggest a lower mortality with the administration of lipid formulations (100). The greatest advantage of lipid formulations is its reduced toxicity as compared to amphotericin B deoxycholate. Overall, the available evidence suggests that voriconazole is more effective than conventional amphotericin B, and that both the lipid formulations of amphotericin B and itraconazole and caspofungin are at least as effective as conventional amphotericin B.

Table 8. Guidelines for antifungal treatment of invasive aspergillosis.

- Documented or probable aspergillosis with CNS involvement, respiratory failure, radiographic image with extensive lung involvement, or evidence of dissemination with severe sepsis criteria: Treatment with caspofungin associated to voriconazole or a lipid formulation of amphotericin B. - Infection by A. terreus or A. flavus[1]: Treatment with voriconazole or caspofungin - Patient not included in the previous groups: Treatment with voriconazole, caspofungin, a lipid preparation of amphotericin B or high doses of amphotericin B deoxycholate (≥1 mg/kg/day)	From 2-3 weeks of treatment, if the clinical course has been favorable and the radiographic image has significantly improved, continued treatment by the oral route with voriconazole or itraconazole may be considered[2]

[1]A. terreus and a high percentage of A. flavus strains are resistant to amphotericin B.

[2]Treatment duration depends on the extent of the condition in the radiographic image, the clinical response, and the persistence of immunosuppression. Treatment must be continued while immunosuppression persists (neutropenia or corticosteroid treatment) and until X rays are normal or a stable residual image is seen. Treatment must be re-started if immunosuppression recurs.

The introduction of caspofungin and voriconazole has also opened the theoretical possibility of an optimized treatment for invasive aspergillosis based on combined therapy, since the association of caspofungin with voriconazole or amphotericin B is often synergistic against *Aspergillus* both *in vitro* (108, 109) and *in vivo* in experimental models (110).

Patients who show at the time of diagnosis a clinical condition associated with a high mortality rate, such as central nervous system involvement, respiratory failure, a radiographic image of the lungs with more than one lobe involved, or evidence of dissemination with severe sepsis criteria probably require a treatment associating voriconazole or a lipid formulation of amphotericin B to caspofungin. For all other

patients not included in the previous group, primary treatment for invasive aspergillosis may consist of administration of voriconazole (by the intravenous route for at least one week, and then by the oral route in a stable patient), other options being a lipid formulation of amphotericin B or caspofungin. From the second or third week of parenteral treatment, if the clinical course is favorable and the radiographic image is significantly improved, a change from parenteral to oral treatment with voriconazole or itraconazole should be considered. If itraconazole is chosen the oral solution must be used, and adequate absorption should be confirmed by regular measurement of serum levels. Treatment is continued for as long as immunosuppression persists and until X-rays are normal or a stable residual image is seen.

Some circumstances related to the causative agent or the infection site may require a change in the selection of antifungal. *Aspergillus terreus* is usually resistant to amphotericin B, and voriconazole (111) or caspofungin would therefore be the drugs of choice. Similarly, some authors have found a high incidence of resistance or a decreased susceptibility to amphotericin B in *Aspergillus flavus*, associated to clinical failure (112), and it thus appears justified to consider the use of voriconazole or caspofungin when the infection is caused by this species. In the event of CNS infection, voriconazole is again particularly attractive, owing to its good penetration in the CNS (113, 114). In such patients, if a lipid formulation of amphotericin B is chosen, the liposomal preparation could be more appropriate, due to its apparent greater efficacy in other fungal infections of the CNS (115, 116).

If the patient does not respond or continues to worsen during the week following the start of any of the monotherapy regimens with voriconazole, caspofungin or amphotericin B, advised for less severe cases, a change to any of the synergistic associations recommended in the previous paragraph for treating the severe forms should be considered. Evaluation of the course of aspergillosis during the first week of antifungal treatment is particularly difficult because the volume of radiographic lesions can experience a highly significant increase that is not necessarily related to an untoward course of the infection (117).

Surgical resection of a pulmonary lesion may sometimes be indicated. This could occur in the event of bleeding, invasion of the pericardium or a large hilar vessel, or progression of the radiographic image despite the recovery of the neutrophil count.

Other measures to be considered, valid to improve the prognosis of any fungal infection, include discontinuation or reduction of treatment with corticosteroids as far as possible. If the patient continues to be neutropenic, the prescription of granulocyte colony stimulating factors could also be considered.

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