Antifungal Therapy in Hematopoietic Stem Cell Transplant Recipients

Alessandro Busca¹ and Livio Pagano²

¹ A.O.U. Città della Salute e della Scienza di Torino, Dipartimento di Oncologia, SSD Trapianto allogenico di cellule staminali, Torino, Italy.
² Istituto di Ematologia, Università Cattolica del Sacro Cuore, Roma

Competing interests: The authors have declared that no competing interests exist.

Abstract. Invasive fungal infections (IFI) represent a major hindrance to the success of hematopoietic stem cell transplantation (HSCT), contributing substantially to morbidity and infection-related mortality. During the most recent years several reports indicate an overall increase of IFI among hematologic patients, in particular, invasive aspergillosis, that may be explained, at least partially, by the fact that diagnoses only suspected in the past, are now more easily established due to the application of serum biomarkers and early use of CT scan. Along with new diagnostic options, comes the recent development of novel antifungal agents that expanded the spectrum of activity over traditional treatments contributing to the successful management of fungal diseases. When introduced in 1959, Amphotericin B deoxycholate (d-AmB) was a life-saving drug, and the clinical experience over 50 years has proven that this compound is effective although toxic. Given the superior safety profile, lipid formulations of AmB have now replaced d-AmB in many circumstances. Similarly, echinocandins have been investigated as initial therapy for IA in several clinical trials including HSCT recipients, although the results were moderately disappointing leading to a lower grade of recommendation in the majority of published guidelines. Azoles represent the backbone of therapy for treating immunocompromised patients with IFI, including voriconazole and the newcomer isavuconazole; in addition, large studies support the use of mold-active azoles, namely voriconazole and posaconazole, as antifungal prophylaxis in HSCT recipients. The aim of the present review is to summarize the clinical application of antifungal agents most commonly employed in the treatment of IFI.

Citation: Busca A., Pagano L. Antifungal therapy in hematopoietic stem cell transplant recipients. Mediterr J Hematol Infect Dis 2016, 8(1): e2016039, DOI: http://dx.doi.org/10.4084/MJHID.2016.039

Published: September 1, 2016
Received: June 30, 2016
Accepted: July 20, 2016

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0), which permits use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Alessandro Busca, A.O.U. Città della Salute e della Scienza di Torino, Dipartimento di Oncologia, SSD Trapianto allogenico di cellule staminali. Corso Bramante 88, 10126 Torino, Italy. Tel: +39 011 6335359, FAX: +39 0116335759. E-mail: abusca@cittadellasalute.to.it

Introduction. Bone marrow, peripheral blood stem cells, and umbilical cord blood transplantation are medical procedures that are widely used to treat diseases once thought incurable. Since the first human bone marrow transplant in the 1950s, over 1 million procedures have been completed worldwide, and the number of transplants performed each year is now close to 70,000. Hematopoietic stem cell transplantation (HSCT) has been used to treat a wide variety of malignant and non-malignant hematological disorders including leukemia, lymphomas, and aplastic anemia, and indications are expanding.

HSCT is a procedure that restores stem cells that have been destroyed by a preparative regimen including chemotherapy with or without total-
body irradiation usually delivered before stem cell infusion to optimize tumor cell kill and, in the case of allogeneic HSCT, immunosuppress the recipient to prevent graft rejection. In addition, allogeneic HSCT recipients may receive immunosuppressive agents, namely calcineurin inhibitors, for a prolonged period after transplant to mitigate the graft-versus-host reaction. According to these considerations, HSCT is associated with a profound immune deficiency resulting in an increased propensity to develop opportunistic infections, in particular, invasive fungal infections (IFI).

Indeed, the last two decades have witnessed an increasing incidence of life-threatening systemic fungal infections in immunocompromised patients, and the epidemiology of IFI in HSCT recipients is undergoing significant changes. Table 1 summarizes the studies published over the last ten years on the epidemiology of IFI in patients receiving HSCT.

The perception of an increase in mold infections has been confirmed by several studies recently published. The epidemiology of invasive aspergillosis (IA) has changed owing to the use of alternative sources of harvested stem cells, new regimens employed to decrease rejection and graft versus host disease (GVHD) and aggressive therapeutic modalities. In patients with autologous HSCT, the frequency of invasive aspergillosis (IA) has decreased due to more rapid engraftment, while the use of peripheral stem cells in allogeneic HSCT may be associated with beneficial engraftment at the theoretical cost of an increased incidence of GVHD. The recipients of cord blood and grafts selected for CD34+ cells have a higher risk for IA early after transplantation. These observations have been confirmed by two recent studies. Girmenia et al. investigated the epidemiology of IFI in a cohort of 1858 allogeneic HSCT recipients showing that grafts from an unrelated donor or umbilical cord blood were associated in multivariate analysis with a high risk of early IFI occurring before day 40. Similarly, Sun et al. demonstrated that the cumulative incidence of IFI in autologous HSCT patients, recipients of HLA-matched related,

Table 1. Epidemiology of invasive fungal infections (IFI) in patients receiving hematopoietic stem cell transplantation (HSCT).

| Reference | Type of study | Timeframe | No. Patients | HSCT | Prophylaxis | IFI rate | mortality |
|-----------|---------------|-----------|--------------|------|-------------|----------|-----------|
| Garcia-Vidal C. CID 2008 (53) | Retrospective 1998-2002 | 1248 | Allo | - | IMI 13.1% | - |
| Pagano L. SEIFEM CID 2007 (54) | Retrospective 1999-2003 | 3228 | Auto 60% Allo 40% | Fluconazole 39% Itraconazole 21% | Auto 1.2% Allo 7.8% | AM Auto 14% AM Allo 77% |
| Mikulska M. BMT 2009 (55) | Retrospective 1999-2006 | 306 | Allo | Fluconazole | IA 15% | AM IA 67% |
| Neofytos D. PATH Alliance CID 2009 (56) | Prospective 2004-2007 | 234 | Auto 31% Allo 69% | - | - | IA 21.5% |
| Kontoyiannis DP. TRANSNET CID 2010 (57) | Prospective 2001-2006 | 875 | Auto Allo | - | Auto 1.2% Allo-MSD 5.8% Allo-MUD 7.7% | - |
| Nucci M. CMI 2013 (58) | Prospective 2007-2009 | 700 | Allo 54% Auto 46% | Fluconazole Allo 81%-Auto 73% | Allo IFI 11.3%- IA 2.3% Auto IFI 1.9%- IA 0% | - |
| Omer AK. BBMT 2010 (59) | Retrospective 2000-2010 | 271 | Allo | Fluconazole 90% | IFI 15% | AM 33% |
| Atalla A TID 2015 (60) | Prospective 2007-2009 | 345 | Allo | Fluconazole 89% | IMI 8.1% | - |
| Girmenia C. GITMO BBMT 2014 (7) | Prospective 2008-2010 | 1858 | Allo | Fluconazole 75% Mold-active 14% | IFI 8.8% | AM 19% |
| Sun Y BBMT 2015 (8) | Prospective 2011 | 1401 | Allo 75% Auto 25% | Fluconazole 61% Itraconazole 22% Voriconazole 19% | Allo 8.9% Auto 4% | Proven IFI 31% Probable IFI 22% |
| Corzo-Leon DE. Mycoses 2015 (61) | Retrospective 2002-2011 | 378 | Allo | Fluconazole Voriconazole | IA 7.9% | IA 52% |
| Liu Y-C. J Mic Imm Infec 2015 (62) | Retrospective 2002-2013 | 421 | Allo | Fluconazole Voriconazole 87% Echinocandin 13% | IFI 7.4% | AM 80% |
| Montesinos P. BMT 2015 (63) | retrospective 2001-2013 | 404 | Allo | Voriconazole 65% Itraconazole 25% No/flucytosine 10% | IFI 11% | - |

Abbreviations: Auto, autologous HSCT; Allo, allogeneic HSCT; AM, attributable mortality; IMI, invasive mold infection; IA, invasive aspergillosis; MSD, matched sibling donor; MUD, matched unrelated donor.
haploidentical, and unrelated HSCT was 3.5%, 4.3%, 13.2% and 12.8% respectively.

Given the high mortality rate reported in this patient population, the early diagnosis of IA remains a clinical challenge: the standard is limited to the correlation of the signs and symptoms of the disease with histopathologic detection of the organism. However, clinical circumstances make this strategy unattainable for many patients. The availability of the newer non-culture-based methods, including noninvasive serologic techniques (galactomannan and β-D-glucan assays) and molecular diagnostics, have become part of the diagnostic strategy in which they are combined with other tools such as the HR-CT scan.\textsuperscript{9}

Along with new diagnostic options, comes the recent development of novel antifungal agents that expanded the spectrum of activity over traditional treatments contributing to the successful management of fungal diseases.

**Antifungal Treatment.** The changing epidemiology of IA in combination to the recent advances in antifungal agents and diagnostic tools facilitating the early recognition of IFI led to redefining the approach to prevention and early treatment of IA in immunocompromised patients.

At the present, four strategies may be identified as follows:

1. **Prophylaxis** may be considered as the first step and consists of the administration of antifungal agents at the onset of a period of high risk of infection, traditionally the beginning of neutropenia or the start of conditioning regimen in HSCT recipients. Antifungal prophylaxis should be considered as a therapeutic option designed to reduce the mortality and morbidity associated with invasive fungal infection, however, even among highly immunocompromised patients, most will not develop an IA.

2. **Empirical treatment** includes the initiation of an antifungal regimen in patients with signs or symptoms suggestive, even not fully documenting IA, and this is typically the case of neutropenic patients with persistent fever (generally 4-7 days in duration) despite the administration of broad-spectrum antibiotics. However, it has become quite clear that fever is a less than an adequate surrogate for evaluating those patients who are in need of antifungal therapy and have IA.

3. **Diagnostic driven therapy** aims to treat IA by radiologic studies and laboratory markers that might be helpful to recognize patients with fungal infection at an early phase of the disease.

4. **Treatment of established infection** applies to those patients who have the diagnosis of a proven fungal infection based on the EORTC/MSG criteria.

**Antifungal Prophylaxis.**

**Meta-analysis studies:** Ziakas et al.\textsuperscript{10} evaluated 20 studies including 4823 patients receiving HSCT. Overall, the risk for IFI while on prophylaxis was 5.1%. The risk of IFI, systemic candidiasis and the need for empiric antifungal treatment was significantly reduced in patients receiving fluconazole compared with patients receiving placebo. Itraconazole was more effective than fluconazole for the prevention of aspergillosis at the expense of more frequent withdrawals. Micafungin was marginally more effective than fluconazole for the prevention of mold infections and IA and reducing the need for empiric antifungal therapy. Voriconazole showed marginally significant effects compared with fluconazole regarding IA and the need for empiric treatment. Voriconazole compared with itraconazole and posaconazole compared with amphotericinB were better regarding empirical antifungal treatment.

Xu et al.\textsuperscript{11} analyzed 17 studies including 5122 patients. The new mold-active agents, namely posaconazole, voriconazole, and micafungin, have reduced the incidence of IFI compared to fluconazole and itraconazole; in addition, posaconazole and voriconazole have reduced transplant-related mortality significantly.

Similarly, Bow et al.\textsuperscript{12} showed that posaconazole, voriconazole reduced the risk of proven/probable IFI compared to fluconazole and itraconazole.

**Clinical Trials:** Table 2 describes the main clinical studies on antifungal prophylaxis in HSCT recipients.

**Fluconazole.** The first prospective randomized study evaluating the efficacy of fluconazole vs. placebo in patients receiving autologous/allogeneic HSCT was published in 1992.\textsuperscript{13} The results of this study showed that 2.8%
Table 2. Studies on antifungal prophylaxis in patients receiving HSCT.

| Reference | Study | HSCT | Study drug | Comparator | Main Results |
|-----------|-------|------|------------|------------|--------------|
| **AZOLES** | | | | | |
| Goodman (13) | Prospective | Allogeneic | Fluconazole 400 mg 179 patients | Placebo 177 patients | IFI: 2.8% fluconazole; 15.8% placebo Fewer IFI-related deaths |
| Slavin (14) | Prospective | Allogeneic | Fluconazole 400 mg 152 patients | Placebo 148 patients | IFI: 7% fluconazole; 18% placebo Better OS with fluconazole |
| Winston (16) | Prospective | Allogeneic | Itraconazole 400 mg 71 patients | Fluconazole 400 mg 67 patients | IFI: 9% itraconazole; 25% fluconazole Fewer IFI-related deaths (9% vs 18%) More GI side effect with itraconazole |
| Marr (17) | Prospective | Allogeneic | Itraconazole 2.5 mg/Kg TID po 151 patients | Fluconazole 400 mg 148 patients | IMI: 5% itraconazole; fluconazole 12% No difference in OS |
| Wingard (18) | Prospective | Allogeneic | Voriconazole 200 mg BID 306 patients | Fluconazole 400 mg 295 patients | No difference in IFI rate |
| Marks (19) | Prospective | Allogeneic | Voriconazole 200 mg BID 234 patients | Itraconazole 200 mg BID 255 patients | No difference in IFI rate Voriconazole better tolerated |
| Ullmann (20) | Prospective | Allogeneic with GVHD | Posaconazole 200 mg TID 291 patients | Fluconazole 400 mg 288 patients | IFI: posaconazole 2%; fluconazole 8% IA: posaconazole 1%; fluconazole 6% |
| Wang (22) | Retrospective | Allogeneic | Posaconazole 200 mg TID 12 patients | Fluconazole 400 mg 40 patients | IFI: 42% fluconazole; posaconazole 8% |
| Winston (21) | Retrospective | Allogeneic | Posaconazole 200 mg TID 106 patients | - | IFI 7.5% |
| Sanchez-Ortega (64) | Prospective | Allogeneic | Posaconazole 200 mg TID 33 patients | Itraconazole 400 mg 16 patients | IFI: posaconazole 0%; itraconazole 12% FFS: posaconazole 91%; itraconazole 56% OS: posaconazole 91%; itraconazole 63% |
| Chafteri (23) | Prospective | Allogeneic | Posaconazole 200 mg TID 21 patients | ABLC 7.5 mg/Kg once/week 19 patients | IFI: posaconazole 0%; ABLC 5% |
| **ECHINOCANDINS** | | | | | |
| Van Burik (24) | Prospective | Allogeneic | Micafungin 50 mg 425 patients | Fluconazole 400 mg 457 patients | IA: micafungin 1.6%; fluconazole 2.4% No difference in OS |
| Hiramatsu (65) | Prospective | Allogeneic | Micafungin 150 mg 52 patients | Fluconazole 400 mg 52 patients | No proven-probable-suspected IFI): 94% micafungin; 88% fluconazole |
| Hashino (66) | Prospective | Allogeneic | Micafungin 100 mg 44 patients | Fluconazole 400 mg 29 patients | IFI: 4/41 micafungin; 10/29 fluconazole |
| Huang (67) | Prospective | Allogeneic | Micafungin 50 mg 136 patients | Itraconazole 2.5 mg/Kg TID po 147 patients | No proven-probable-suspected IFI: 94% micafungin; 88% fluconazole |
| El-Cheikh (68) | Prospective | Allogeneic (Haploidentical) | Micafungin 50 mg 26 patients | - | No IFI |
| Chou (69) | Retrospective | Allogeneic | Caspofungin 35-50 mg 123 patients | - | IFI: 7.3% |
| **POLYENES** | | | | | |
| Luu Tran (27) | Prospective | Allogeneic with GVHD | L-AmB 3 mg/Kg once/week 16 patients | Echinocandins: 12 patients | IFL: L-AmB 19%; Echinocandins 17% Triazoles 7% |
| El-Cheikh (26) | Retrospective | Allogeneic with GVHD | L-AmB 7.5 mg/Kg once/week 42 patients | Other antifungal prophylaxis 83 patients | IFL 8% vs 36% IFL-related deaths 0% vs 14% |
| Koh (70) | Prospective | Allogeneic | D-AmB 0.2 mg/Kg 86 patients | Fluconazole 200 mg 100 patients | IFL: 12% fluconazole; 12.8% D-AmB No difference in OS IFL-related deaths 6% fluconazole; 7% D-AmB |

Abbreviations: L-AmB, Liposomal Amphotericin B; D-AmB, deoxycholate Amphotericin B; ABLC, Amphotericin B lipid complex; IFI, invasive fungal infection; OS, overall survival; GI, gastrointestinal; FFS, fungal-free survival.

The reduced rate of infection for the fluconazole group resulted in fewer IFI-related deaths (1/179 patients receiving fluconazole developed IFI, compares to 15.8% of those receiving placebo.)
vs. 10/177; p<0.001), although there was no difference in the overall survival.

Another prospective randomized, double-blind study examined the efficacy of fluconazole 400 mg given prophylactically for 75 days post-transplant (autologous and allogeneic HSCT) compared to placebo. The results of this study showed that the rate of systemic fungal infections was significantly lower in the fluconazole arm as compared to placebo-treated patients (7% vs. 18%, p=0.004). The results of this study demonstrated an overall mortality benefit, as 17.5% more patients in the fluconazole arm survived until eight years after related and unrelated HSCT, and was the first to show that the prophylaxis with fluconazole is capable in patients allografted not only to prevent infections but also to affect the survival.

Itraconazole. An open-label, multicenter randomized trial comparing the efficacy and safety of itraconazole with fluconazole in 140 patients receiving an allogeneic HSCT was published in 2003. The results of this study showed that itraconazole resulted in fewer proven IFI (9% vs. 25%, p=0.01) and fewer deaths were related to fungal infection in patients given itraconazole (9%) than in patients given fluconazole (18%, p=0.13). More frequent gastrointestinal side effects were observed in patients given itraconazole as compared to fluconazole (24% vs. 9%).

The Seattle group reported the results of a large trial in 304 patients receiving an allogeneic HSCT, who were randomized to receive fluconazole (400 mg/day) or itraconazole (oral solution or iv) for 180 days after HSCT. The cumulative incidence of proven or probable IFI was not different between the two arms (fluconazole 16% vs. itraconazole 13%, p=0.46). Itraconazole provided better protection against invasive mold infections (fluconazole 12% vs. itraconazole 5%, p=0.03), but similar protection against candidiasis (3% vs. 2%, p=0.69), however, no survival benefit was seen with itraconazole. More patients in the itraconazole arm developed hepatotoxicities, and more patients discontinued the drug because of toxicities or gastrointestinal intolerance (36% vs. 16%, p< 0.001).

Voriconazole. Wingard et al. published the results of a prospective randomized trial comparing voriconazole (200 mg BID iv/po for 100 days or 180 days in case of steroid treatment) vs. fluconazole (400 mg QD) in allogeneic HSCT recipients. The incidence of proven-probable or presumptive IFI was not different between the two arms, while the incidence of aspergillosis was marginally reduced in patients who received voriconazole. A subgroup analysis of patients with AML showed a significantly reduced incidence of IFI (8% vs. 21%, p 0.04) and a better fungal-free survival (78% vs. 61%, p 0.04) in patients receiving voriconazole.

Similar results have been reported in a second study comparing itraconazole and voriconazole. The incidence of IFI and overall survival were superimposable in the two treatment arms (voriconazole 1.3% vs. itraconazole 2%), while patients in the itraconazole group were able to receive the drug at least 30 days less than patients in the voriconazole group.

Posaconazole. This agent has been compared with oral fluconazole for prophylaxis of IFI in 600 patients with grade II-IV acute GVHD or extensive chronic GVHD (20). The incidence of IFI was not significantly different in the two study groups (5.3% posaconazole vs. 9% fluconazole, p=0.07), while posaconazole prophylaxis resulted in a lower number of invasive aspergillosis (2.3% posaconazole vs. 7% fluconazole, p=0.006). The mean time to onset of invasive fungal infection was 102 days in the posaconazole arm and 88 days in the fluconazole arm. The number of deaths due to proven or probable IFI was lower in the posaconazole group than in the fluconazole group (1% vs. 4%, p=0.46), although the overall mortality was similar in the two groups.

Several real life (retrospective) studies have been subsequently published, confirming the efficacy of prophylaxis with posaconazole in the setting of allogeneic HSCT.

Echinocandins. A large number of studies have evaluated the efficacy of different echinocandins to prevent IFI in patients receiving HSCT.

The efficacy and safety of micafungin have been investigated in a large randomized, double-blind, comparative phase III trial for the prophylaxis of IFI in HSCT patients in comparison with fluconazole. Overall, the efficacy defined as the absence of proven-probable-suspected IFI was greater with micafungin than with fluconazole (80% vs. 73%, p 0.03). There was a nonsignificant trend toward a reduced incidence of invasive aspergillosis, although the absolute number of events was remarkably low in both arms (n=1
micafungin; n=7 fluconazole), possibly due to the inclusion of a large proportion of low-risk patients (70% autologous HSCT). Empirical antifungal therapy was required in fewer patients treated with micafungin than with fluconazole (15.1% versus 21.4%, respectively; p = 0.024).

Subsequent studies have confirmed the efficacy of micafungin in comparison to standard azoles (Table 2). One issue arising from published studies is the optimal dose of micafungin for prophylaxis of IFI in HSCT recipients. In fact, different dosages have been used in clinical trials, spanning from 50 mg up to 150 mg per day. Lagebrake et al.25 have analyzed the dose of 50 mg, 100 mg, 150 mg of micafungin as antifungal prophylaxis: the rate of IFI did not result different according to the doses, nor was different the incidence of side effect; a nonsignificant trend toward a greater need for empirical treatment has been observed with the lowest dose of 50 mg.

Polynenes. The role of polynenes as antifungal prophylaxis in HSCT recipients has been investigated in few studies (Table 2). El-Cheikh et al.26 reported the results of a retrospective study in which liposomal-Amphotericin B (L-AmB), administered at the dose of 7.5 mg/Kg once a week in patients with acute or chronic GVHD, was compared to a historical control group of patients who received different prophylactic regimens (fluconazole in 71% of the cases). The incidence of IFI was reduced (8% vs. 36%, p 0.008) as well as the fungal related mortality (0% vs. 14%, p 0.005) in patients who received L-AmB, while overall survival was not statistically different. Otherwise, Luu Tran27 et al., did not find any significant benefit with the use of L-AmB (3 mg/Kg one a week) when compared to echinocandins and triazoles.

According to the published studies, several guidelines have provided recommendations on antifungal prophylaxis in patients candidates to HSCT (Table 3).

**Empirical Treatment.** The rationale for empiric antifungal therapy is based on autopsy studies showing the role of IFI as the cause of death in neutropenic patients28 and on clinical observations defining the importance of early treatment in the prognosis of IFI.29 These findings were supported by several studies showing a decreased mortality due to IFI in patients receiving empiric AmB as compared with historical controls where antifungal therapy was initiated upon documentation.30-33

The first evidence that empiric antifungal treatment in neutropenic patients with a persistent fever might have beneficial effects has been shown in two prospective studies published in early ’8034 comparing deoxycholate-AmB (d-AmB) versus no therapy. Nevertheless, these

---

**Table 3.** Strength of recommendation on antifungal prophylaxis in allogeneic HSCT recipients

| Pre-Engraftmen Phase | Post-engraftment Phase/GVHD |
|----------------------|-----------------------------|
|                      | ECIL-5 2013 | ESCMID 2014 | DGHO 2014 | GITMO 2014 | NCCN 2015 | ECIL-5 2013 | ESCMID 2014 | DGHO 2014 | GITMO 2014 | NCCN 2015 |
| **Fluconazole**      |            |            |            |            |           |            |            |            |            |           |
| 400 mg QD            | A I        | -          | B I        | A I        | 1          | A III      | -          | -          | -          | -          |
| **Itraconazole**     |            |            |            |            |           |            |            |            |            |           |
| 400 mg QD            | B I        | D I        | C I        | -          | 2 B        | B I        | C II       | C I        | -          | -          |
| **Posaconazole**     |            |            |            |            |           |            |            |            |            |           |
| Oral sol 200 mg q8th | B II       | B II       | B II       | -          | 2 B        | A I        | A I        | A I        | A I        | 1          |
| Tab 300 mg QD        | B II       | -          | B II       | -          | 2 B        | A I        | -          | A II       | -          | 1          |
| **Voriconazole**     |            |            |            |            |           |            |            |            |            |           |
| 200 mg q12h          | B I        | C I        | B I        | B I        | 2 B        | B I        | C II       | C II       | B I        | 2 B        |
| **Caspofungin**      |            |            |            |            |           |            |            |            |            |           |
| 50 mg QD             | No data    | -          | -          | -          | -          | -          | -          | -          | -          | C III      |
| **Micafungin**       |            |            |            |            |           |            |            |            |            |           |
| 50 mg QD             | B I LR-mold| C I HR-mold| C II       | B I        | B I        | 1          | C II       | C III      | C II       | C III      |
| **L-AmB**            |            |            |            |            |           |            |            |            |            |           |
| Areosol AmB          | C III      | -          | -          | C I II      | 2 B        | C II       | -          | -          | C III      | -          |

---

ECIL-5: [www.kobe.fr/ECIL5antifungalprophylaxis](www.kobe.fr/ECIL5antifungalprophylaxis)
ESCMID: [www.escmid.org](www.escmid.org)
DGHO: TaCke D, Büchheidt D, Karthaus M. et al.Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Ann Hematol 2014, 93:1449–1456
GITMO: Ref 7
NCCN: [www.NCCN.org](www.NCCN.org)

---
studies, when re-evaluated on the basis of the current knowledge, may be largely criticized and do not have the statistical power necessary to detect differences between the groups analyzed.

A consistent number of studies have analyzed the efficacy of different compounds used as an empirical treatment in hematologic patients with neutropenic fever, but none of these studies included HSCT recipients only (Table 4).

**Azoles.** Three studies have compared fluconazole to AmB for empiric antifungal therapy in immunocompromised patients. Two of them included few patients, while the third included 317 neutropenic patients with persistent or recrudescent fever despite 4 or more days of antibacterial therapy who were randomly assigned to receive either fluconazole (400 mg intravenously once daily) or d-AmB (0.5 mg/kg once daily). A satisfactory response (at the end of therapy if the patient was afebrile, had no clinical or microbiological evidence of fungal infection, and did not require study termination due to lack of efficacy, drug toxicity, or death) occurred in 68% of the patients treated with fluconazole and in 67% of patients treated with d-AmB. Progressive or new fungal infections during therapy occurred in 13 (8%) patients treated with fluconazole and in 10 (6%) patients treated with d-AmB. Adverse events related to study drug occurred more often in patients treated with d-AmB (81%) than patients treated with fluconazole (13%, \( P = 0.001 \)). Overall mortality (17% of patients treated with fluconazole versus 21% of patients treated with d-AmB) and mortality from fungal infection (4% of patients treated with fluconazole versus 3% of patients treated with d-AmB) were similar in each study group.

Itraconazole has been compared to conventional AmB in 384 neutropenic patients with cancer. The overall response rate was 47% in the itraconazole group and 38% in the AmB group, but fewer drug-related adverse events occurred in the itraconazole group than the AmB group.

**Table 4.** Clinical trials comparing antifungal agents as empiric antifungal therapy in patients with febrile neutropenia

| Author/year | Study drugs | No. patients | IFI | Success rates |
|-------------|-------------|--------------|-----|---------------|
| **d-AmB vs no Therapy** | | | | |
| Pizzo, 1982 (34) | d-AmB antibiotics | 18 | 6% | ND |
| EORTC, 1989 (35) | No Tx | 16 | 0% |
| | d-AmB antibiotics | 68 | 1% | 69% |
| | | 64 | 9% | 53% |
| **Azoles** | | | | |
| Viscoli, 1996 (71) | Fluco d-AmB antibiotics | 56 | ND | 75% |
| Malik, 1998 (36) | Fluco d-AmB antibiotics | 56 | ND | 56% |
| Winston, 2000 (37) | Fluco d-AmB antibiotics | 107 | 8% | 68% |
| | | 106 | 6% | 67% |
| **Itra vs d-AmB** | | | | |
| Boogaerts, 2001 (38) | Itra d-AmB | 192 | 3% | 47% |
| | | 192 | 3% | 38% |
| **Vorico vs L-AmB** | | | | |
| Walsh, 2002 (39) | Vorico L-AmB | 415 | 1.9% | 26% |
| | | 422 | 5% | 31% |
| **AmB lipid formulations** | | | | |
| Walsh, 1999 (40) | L-AmB d-AmB | 343 | 3% | 50% |
| Prentice, 1997 (41) | d-AmB 1 mg/Kg | 102 | 2% | 49% |
| | L-AmB 1 mg/Kg | 118 | 2.6% | 58% |
| | L-AmB 5 mg/Kg | 118 | 1.7% | 64% |
| | ABLC 5 mg/Kg/d | 78 | 3.8% | 33% |
| | L-AmB 3 mg/Kg/d | 85 | 3.6% | 40% |
| | L-AmB 5 mg/Kg/d | 81 | 2.5% | 42% |
| **ABLC vs L-AmB** | | | | |
| Wingard, 2000 (72) | ABLC L-AmB | 556 | 5% | 34% |
| | | 539 | 4% | 34% |

**Abbreviations:** AmB, amphotericin-B; d-AmB, amphotericin-B deoxycholate; ND, not documented; L-AmB, liposomal AmB; ABLC, amphotericin B lipid complex; fluco, fluconazole; itra, itraconazole; vorico, voriconazole.
group (5% vs. 54%, p=0.001). Breakthrough fungal infections occurred in 5 patients in each group. In conclusion, the results of this study demonstrated that itraconazole and AmB have equivalent efficacy as empirical antifungal therapy. However, itraconazole is associated with significantly less toxicity.

Voriconazole has been compared to L-AmB in a prospective randomized multi-institutional trial. Analysis of the 5 composite end points (no breakthrough fungal infections; survival 7 days after end of therapy; no discontinuation of therapy prematurely; resolution of fever during neutropenia; complete or partial response of patients with baseline fungal infections) favoured L-AmB for all variables except the prevention of breakthrough fungal infections (1.9% in the voriconazole group vs 5% in the L-AmB group, p=0.02). A subgroup analysis of patients receiving an allogeneic HSCT (18% of the patients in both study groups) showed that breakthrough fungal infections occurred in 1.4% of the patients treated with voriconazole and 9.2% of the patients treated with L-AmB. Overall success rates were 23.7% in the voriconazole group and 30% in the L-AmB group, however, voriconazole did not fulfill the protocol-defined criteria for noninferiority to L-AmB with respect to overall response to empirical therapy.

AmB lipid formulations. In 1999, Walsh et al. first challenged the assumption that conventional AmB is the optimal antifungal treatment for patients with persistent fever, in a large randomized trial including 702 patients with persistent fever and neutropenia. L-AmB was as effective as d-AmB when success was analyzed on the basis of the composite five end points: the rates of successful treatment were similar (L-AmB 50% vs. d-AmB 49%) as well as survival (L-AmB 93% vs. d-AmB 90%), resolution of fever (58% in both groups) and discontinuation of the study drug (L-AmB 14% vs. d-AmB 19%); by contrast, there were fewer breakthrough fungal infections among patients receiving L-AmB (3%) than among those who received d-AmB (8%). With L-AmB fewer patients had infusion-related toxicity and nephrotoxicity. It should be underscored that several aspects of this study have been criticized, including the fact that d-AmB was administered at a low dose (0.6 mg/Kg/d) and the absence of salt loading for prevention of d-AmB nephrotoxicity.

In 1997 Prentice and coworkers published the results of two prospective open-label randomized trials comparing d-AmB at the dose of 1 mg/Kg/d (102 patients) with L-AmB 1 mg/Kg/d (L-AmB 1:118 patients) and L-AmB 3 mg/Kg/d (L-AmB 3:118 patients) for empirical treatment of fever in neutropenic adults and children. Efficacy was defined as defervescence without the development of new fungal infections. Patients who received L-AmB had a 2-6-fold decrease in the incidence of drug-related side effects (p < 0.01). More importantly, treatment success was observed in 49% of patients in the d-AmB arm, 58% and 64% of L-AmB 1 and L-AmB 3 arms respectively (p=0.09); L-AmB 3 was significantly more efficacious than d-AmB (p=0.03).

Echinocandins. Caspofungin has been tested for empirical antifungal therapy in the setting of a double-blind, non-inferiority study design where the study drug has been compared to L-AmB in 1123 patients. Caspofungin was found to be non-inferior to L-AmB (overall success rate 33.9% for caspofungin vs. 33.7% for L-AmB), with an advantage among patients with baseline documented infections (successful treatment 52% vs. 26% respectively); the proportion of patients who survived 7 days after therapy was greater in the caspofungin group (93% vs. 89% respectively) and premature study discontinuation for toxicity or lack of efficacy occurred less often in the caspofungin group than in the L-AmB group (10% vs 14% respectively). In a subgroup analysis of patients who received an allogeneic HSCT, a favorable response was observed in 43% of the patients treated with caspofungin and 37% of the patients treated with L-AmB. The excellent toxicity profile of caspofungin was demonstrated in this study: fewer patients had a nephrotoxic effect (3% vs. 11% respectively) and infusion-related events (35% vs. 52% respectively).

Diagnostic-Driven Therapy (DDT). The development of non-cultured based microbiological and radiological diagnostic tests that are rapid, sensitive and specific made possible an earlier diagnosis of IA. The incorporation of these tests in the routine management of neutropenic patients has the potential for targeting patients in true need of antifungal therapy. According to these statements, DDT aims to treat a suspected early IFI on the basis of radiologic
studies, laboratory markers or both rather than fever alone.

The potential impact of this therapeutic approach has been explored in several studies, where antifungal treatment has been guided by the galactomannan test (GM),

\[ \text{PCR, } CT \text{ imaging, } \text{clinical criteria} \]

or a combination of clinical work-up and diagnostic tests.

However, only a minority of these studies refer to patients receiving HSCT. Dignan FL et al.\(^{45}\) used an early treatment strategy based on CT scan in 99 allogeneic HSCT recipients. Interestingly, 17% of the patients received antifungal therapy based on radiologic imaging compared to 54% of the patients who would have received antifungal treatment if an empirical approach was used. Similar results have been reported by Oshima K et al.\(^{49}\) with the use of a treatment strategy in which antifungal agents were initiated when patients had a positive serum test and/or radiologic imaging suggestive of IFI. Hebart et al.\(^{44}\) performed a randomized trial comparing PCR-based treatment and empirical antifungal therapy with L-AmB in 408 patients undergoing allogeneic HSCT. Patients randomized to PCR-based strategy had PCR screening planned twice weekly while inpatients and once weekly after discharge until day +100. L-AmB was initiated in those cases with two consecutive positive PCR results and in the empirical treatment group after five days of febrile neutropenia not responding to broad-spectrum antibiotics. Eleven patients in the PCR-based strategy were diagnosed with IFI compared with 16 in the empirical treatment group. A reduction in early mortality was documented until day +30 for patients receiving PCR-based antifungal therapy (4 deaths vs. 13 deaths in the empirical treatment group, p=0.03).

Treatment of established invasive aspergillosis. Several studies evaluated the efficacy of different antifungal agents in patients with hematologic malignancies, but the number of HSCT recipients included in these studies, ranges between 20-30%, except one study analyzing the efficacy of caspofungin (Table 5).

Herbrecht et al.\(^{50}\) evaluated Caspofungin as first-line therapy of proven-probable IA in 24 allogeneic HSCT recipients. Among the 24 eligible patients, a favorable response was reported in 42% of the cases, and overall survival at 12 weeks was 50%. Although these results may seem disappointing, responses compare favorably to those reported with the use of voriconazole (overall response 32%) and L-AmB (overall response 47%) in the subgroup of patients receiving HSCT.

More recently, Marr et al.\(^{51}\) evaluated the safety and efficacy of voriconazole combined with Anidulafungin compared with voriconazole monotherapy for the treatment of IA. Mortality rates at six weeks were 19.3% for combination therapy and 27.5% for monotherapy (p 0.087). In a post hoc analysis of patients with a diagnosis of invasive fungal infection, 71% of patients received antifungal therapy (4 deaths vs. 13 deaths in the empirical treatment group, p=0.03).

### Table 5. Summary of the studies analyzing first-line antifungal therapy in hematologic patients.

| Study                        | Herbrecht NEJM 2002 (50) | AMBILOAD Cornely CID 2007 (73) | EORTC Herbrecht BMT 2010 (74) | COMBO Vori+Anidula 2015 (51) | SECURE Maertens Lancet 2015 (52) |
|------------------------------|-------------------------|--------------------------------|--------------------------------|-------------------------------|---------------------------------|
| No. patients                 | 144                     | 133                            | 107                            | 24                            | 135                             |
| Median age                   | 48                      | 50                             | 51                             | 50                            | 64                              |
| Acute leukemia               | 40%                     | 45%                            | 51                             | 50                            | 64                              |
| Allogeneic HSCT              | 26%                     | 23%                            | 16%                            | 100%                          | 0                               |
| Favourable response          | 53%                     | 32%                            | 50%                            | 42%                           | 33%                             |
| Survival at 12 weeks         | 71%                     | 58%                            | 72%                            | 50%                           | 53%                             |

**Abbreviations:** Vori, voriconazole; D-AmB, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B; Caspo, caspofungin; Anidula, anidulafungin; Isavuc, isavuconazole.
based on radiological abnormalities and GM positivity, the 6-week mortality was significantly lower in combination therapy compared to monotherapy 15.7% vs. 27.3%, p 0.037). The safety profile was similar in the two treatment groups.

Isavuconazole is a new extended-spectrum prodrug triazole with efficacy for IA and mucormycosis. The SECURE study\(^5\) was a randomized, double-blind trial which evaluated the noninferiority of isavuconazole compared with voriconazole for the primary treatment of IFI. The majority of patients had an underlying hematologic malignancy (82% isavuconazole; 86% voriconazole). The primary end point of crude all-cause-mortality at six weeks was 18.6% in the isavuconazole arm and 20.2% in the voriconazole arm, demonstrating noninferiority of isavuconazole to voriconazole. Significantly fewer patients reported events considered drug-related by the investigator for isavuconazole than for voriconazole (42% vs. 60%; p<0.001).

Based on the published studies, the ECIL-6 guidelines assigned the higher strength of recommendation to voriconazole, isavuconazole (both Al) and L-AmB (B1); ABLC received BII, caspofungin CII and the combination voriconazole-anidulafungin CI.

### References:

1. Pagano L, Caira M, Nosari A et al. Fungal Infections in Recipients of Hematopoietic Stem Cell Transplants: Results of the SEIFEM B-2004 Study—Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. Clinical Infectious Diseases 2007; 45:1161-70. [PMid:17918077]
2. Fukuda, T., M. Boeckh, R. A. Carter, B. M. Sandmaier, M. B. Maris, and D. G. Maloney. 2003. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood 102:827-833. [PMid:12689933]
3. Marr, K. A., R. A. Carter, M. Boeckh, P. Martin, and L. Corey. 2002. Invasive aspergillosis in allogeneic stem cell transplant recipients; changes in epidemiology and risk factors. Blood 100:4338-4366. [PMid:12393425]
4. Powles, R., J. Mehta, S. Kulikani, J. Treleaven, B. Millar, J. Marsden, V. Shepherd, A. Rowland, B. Sirohi, D. Tait, C. Horton, S. Long, and S. Singhal. 2000. Allogeneic blood and bone-marrow stem-cell transplantation in haematological malignant diseases: a randomised trial. Lancet 355:1231-1237. [PMid:10.1182/blood-2003-02-0456]
5. Grew, W. B., J. S. Moreb, D. Rogue, K. Manion, H. Leather, V. Reddy, S. A. Kahan, K. J. Finnewicz, H. Nguyen, C. J. Clancy, P. S. Mehta, and J. R. Wingard. 2002. Late onset of invasive Aspergillus infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant. 29: 15-19. [PMid:11840139]
6. Bensinger, W. I. 2000. Blood or marrow? Lancet 355:1199-1200. [PMid:10.1182/blood-2000-02-0808]
7. Girmenia C, Raiola AM, Picciocchi A, et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Grupo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transplant. 2014;20:872-80. [PMid:24631738]
8. Sun Y, Meng F, Han M. Epidemiology, Management, and Outcome of Invasive Fungal Disease in Patients Undergoing Hematopoietic Stem Cell Transplantation in China: A Multicenter Prospective Observational Study. Biol Blood Marrow Transplant 2015, 21:1117-1126. [PMid:25840339]
9. Busca A, Localelli F, Barbui A, Limerutti G, Serra R, Libertucci D, Falda M. Usefulness of sequential aspergillus galactomannan antigen detection combined with early radiologic evaluation for diagnosis of invasive pulmonary aspergillus in patients undergoing allogeneic stem cell transplantation. Transplantation Proceeding 2006,38(5):1610. [PMid:16797366]
10. Ziaqas PD, Kourbeti IMylonakis E, Systemic Antifungal Prophylaxis After Hematopoietic Stem Cell Transplantation: A Meta-Analysis. Clinical Therapeutics 2014, 36: 292-307. [PMid:24439393]
11. S-X. Xu, J.-L. Shen, X.-F. Tang, and B. Feng Newer Antifungal Agents for Fungal Infection Prevention During Hematopoietic Cell Transplantation: A Meta-Analysis. Transplantation Proceedings 2013, 45: 407-414. [PMid:23375330]
12. Bow EJ, Vanness DJ, Slavin M et al. Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients. BMC Infectious Diseases 2015, 15:1-11. [PMid:25887385]
of once weekly liposomal amphotericin B for the prevention of invasive fungal infections in hematopoietic stem cell transplant patients with graft-versus-host disease. J Oncol Pract 2014; 10: 1-7

28. Bodey, G.P. (1986) Fungal infection and fever of unknown origin in neutropenic patients. American Journal of Medicine, 1986;80: 112-119. PMid:122006

29. Aisner, J., Wiernik, P.H. & Schimpff, S.C. Treatment of invasive aspergillosis: relation of early diagnosis and treatment to response. Annals of Internal Medicine 1977, 86: 539-543. http://dx.doi.org/10.1001/anninternmed.1977.01550170012002

30. DeGregorio, M.W., Lee, W.M., Linker, C.A., Jacobs, R.A. & Ries, C.A. Fungal infections in patients with acute leukemia. American Journal of Medicine, 1982,73: 543-548. http://dx.doi.org/10.1016/0002-9348(82)90334-5

31. Holleran, W.M., Wilbur, J.R. & DeGregorio, M.W. Empiric amphotericin B therapy in patients with acute leukemia. Reviews of Infectious Disease 1985, 7: 619-624. http://dx.doi.org/10.1093/clinids/7.5.619

32. Stein, R.S., Kayser, J. & Flexner, J.M. Clinical value of empirical amphotericin B in patients with acute myelogenous leukemia. Cancer 1982, 50: 2247-2251. http://dx.doi.org/10.1002/1097-1944(19821201)50:2<2247::AID-CNCR2820501013>3.0.CO;2-S

33. Karp, J.E., Metz, W.G. & Charache, P. Response to empirical amphotericin B during antileukemic therapy-induced granulocytopenia. Reviews of Infectious Disease 1991, 13: 592-599. http://dx.doi.org/10.1093/clinids/13.4.592

34. Pizzo PA, Robichaud KJ, Gill FA, Witteksy FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982;72:101-111. http://dx.doi.org/10.1016/0002-9348(82)90594-0

35. The EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. Am J Med 1989;86:668-72. http://dx.doi.org/10.1016/0002-9348(89)90415-5

36. Malik IA, Mod I, Aziz Z, Khan S, Saleman M. A Randomized Comparison of Fluconazole with Amphotericin B as Empiric Antifungal Agents in Cancer Patients with Prolonged Fever and Neutropenia. Am J Med. 1998;105:478-483. http://dx.doi.org/10.1016/S0002-9348(97)00252-X

37. Winston DJ, Hathorn IW, Schuster MG, Schiller GJ, Territo MC. A Multicenter, Randomized Trial of Fluconazole versus Amphotericin B for Empiric Antifungal Therapy of Febrile Neutropenic Patients with Cancer. Am J Med. 2000;108:282-289. http://dx.doi.org/10.1016/S0002-9348(99)00547-X

38. Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: a randomized, controlled trial. Ann Intern Med 2001;135:412-22. http://dx.doi.org/10.1056/NEJM200109183451601

39. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002;346:225-34. http://dx.doi.org/10.1056/NEJMoa0125311 PMid:11807126 X

40. Walsh TJ, Finberg RW, Arndt K, et al. Liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 1999;340:764-71. http://dx.doi.org/10.1056/NEJM199901133580101

41. Prentice, H.G., Hann, L.M., Herbrecht, R., Aoun, M., Kvaloy, S., Catovsky, D., Pinkerton, C.R., Schey, S.A., Jacobs, F., Oakhill, A., Stevens, R.F., Darbishire, P.J., Gibson, B.E.A randomization comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. British Journal of Haematology 1997;98:711-718. http://dx.doi.org/10.1046/j.1365-2141.1997.07296.x

42. Walsh TJ, Teppler H, Donowitz GR et al. Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia. N Engl J Med 2004;351:1391-402. http://dx.doi.org/10.1056/NEJMoa040446 PMid:1549300

43. Maertens, J., Theunissen, K. and Verhoef, G. Galactomannan and computed tomography-based pre-emptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: A prospective feasibility study. Clin Infect Dis 2005;41:1242-1250. http://dx.doi.org/10.1086/442231 PMid:15546073

44. Hebart H, Klingersp L, Klingebiel T et al., A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after Allo-SCT. Bone Marrow
Transplantation 2008, 1-9
Nucci M, Fevola SO, Ethell ME et al. An early CT-diagnosis-based treatment strategy for invasive fungal infection in allogeneic transplant recipients using caspofungin first line: an effective strategy with low mortality. Bone Marrow Transplantation 2009, 1-6
http://dx.doi.org/10.1038/bmt.2008.427

Aguiar-Guisado M, Martin-Pe-a, Espigado I et al. Universal antifungal therapy is not needed in persistent febrile neutropenia: a tailored diagnostic and therapeutic approach. Haematologica 2012;97:464-71.
http://dx.doi.org/10.3324/haematol.2011.049999
PMid:22058202
PMCID:PMC3291604

Grimesia C, Micozzi A, Gentile G, Santilli S, Arleo E, Cardarelly L, et al. Clinically driven diagnostic antifungal approach in neutropenic patients: a prospective feasibility study. J Clin Oncol. 2010;28:667-74.
http://dx.doi.org/10.1200/JCO.2009.21.8032
PMid:19841328

Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F, et al. Empirical versus preemptive antifungal therapy for highrisk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis 2009;48(8):1042-51.
http://dx.doi.org/10.1086/597395
PMid:19281327

Oshima K, Kanda Y, Asano-Mori Y et al. Presumptive treatment strategy for aspergillosis in allogeneic haematopoietic stem cell transplant recipients. Journal of Antimicrobial Chemotherapy 2007, 60: 350-355
http://dx.doi.org/10.1093/jac/dkm217
PMid:17584800

Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002 Aug 8;347:408-15.
http://dx.doi.org/10.1056/NEJMoa0201911
PMid:12167683

Marr KA, Schlamm HT, Herbrecht R et al. Combination Antifungal Therapy for Invasive Aspergillosis. A Randomized Trial. Ann Intern Med. 2015;162:81-89.
http://dx.doi.org/10.7326/M13-2508
PMid:25599346

Maertens JA, Raad II, Marr KA et al. Itraconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016, 387:760-9.
http://dx.doi.org/10.1016/S0140-6736(15)31599-9

Garza-Vidal C, Upton A, Kirby KA, A Marr KA. Epidemiology of Invasive Mold Infections in Allogeneic Stem Cell Transplant Recipients: Biological Risk Factors for Infection According to Time after Transplantation. Clinical Infectious Diseases 2008; 47:1041-50
http://dx.doi.org/10.1086/591969
PMid:18781877
PMCID:PMC2668264

Pagano L, Caira M, Nosari A et al. Fungal Infections in Recipients of Hematopoietic Stem Cell Transplants: Results of the SEIFEM B-2004 Study–Sorveglianza Epidemiologica Infettiva Fungine Nelle Ematopoietica Maligaine. Clinical Infectious Diseases 2007; 45:1161-70.
http://dx.doi.org/10.1086/522189
PMid:17918077

Mikulska M, Raioa AM, Bruno B, et al. Risk factors for invasive aspergillosis and related mortality in recipients of allogeneic SCT from alternative donors: an analysis of 306 patients. Bone Marrow Transplantation 2009, 44;361-370
http://dx.doi.org/10.1038/bmt.2009.39
PMid:19308042

Neofytos D, Horn D, Anaissie E et al. Epidemiology and Outcome of Invasive Fungal Infections in Patients Undergoing Hematopoietic Stem Cell Transplant. Biol Blood Marrow Transplant 2012,18: 1509
http://dx.doi.org/10.1016/j.bbmt.2012.03.014
PMid:22469284

El Choikh J, Vincent G, Crocirolo R et al. Efficacy and safety of micafungin for prophylaxis of invasive fungal infections in patients undergoing haplo-identical hematopoietic SCT. Bone Marrow Transplantation 2013, 1-6
http://dx.doi.org/10.1038/bmt.2013.87

Chou LS, Lewis RE, Ippoliti C et al. Caspofungin as Primary Antifungal Prophylaxis in Stem Cell Transplant Recipients. Pharmacotherapy 2007; 27:1644-1650
http://dx.doi.org/10.1592/phco.27.12.1644
PMid:18041885

Koh LP, Kupur A, Goh YT, Fook-Chong SMC, Tan PH. Randomized Trial of Fluconazole Versus Low-Dose Amphotericin B in Prophylaxis Against Fungal Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation. American Journal of Hematology 2002;71:260-267.
http://dx.doi.org/10.1002/ajh.10234
PMid:12447954

Viscoli C, Castagnola E, Van Lint MT, et al. Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial. Eur J Cancer 1996;32:814-20.
http://dx.doi.org/10.1007/s12185-008-0196-y
PMid:19039629

Wingard JR, White MH, Anaissie E et al. A randomized double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. CID 2000, 31:1155-1163
http://dx.doi.org/10.1093/infdis/31.11.1155
PMid:11064962

Comely OA, Maertens J, Bresnik M et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmbiLoad trial). Clin Infect Dis. 2007 44:1289-97.
http://dx.doi.org/10.1086/513431
PMid:17443465

Herbrecht R, Maertens J, Bala L et al. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study. Bone Marrow Transplantation 2010 45, 1277
http://dx.doi.org/10.1038/bmt.2009.334
PMid:20662933

Viscoli C, Herbrecht R, Akan H et al. An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. Journal of Antimicrobial Chemotherapy 2009 64, 1274
http://dx.doi.org/10.1093/ijac/dxp355
PMid:19841031