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Review

Primary Prophylaxis of Invasive Fungal Diseases in Allogeneic Stem Cell Transplantation: Revised Recommendations from a Consensus Process by Gruppo Italiano Trapianto Midollo Osseo (GITMO)

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A B S T R A C T

This document updates and expands the recommendations on primary prophylaxis of invasive fungal diseases (IFD) in allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients, published in 2009 by the Gruppo Italiano Trapianto Midollo Osseo (GITMO). A consensus process was undertaken to describe and evaluate current information and practice regarding risk stratification and primary antifungal prophylaxis during the pre-engraftment and postengraftment phases after allo-HSCT. The revised recommendations were based on the evaluation of recent literature including a large, prospective, multicenter epidemiological study of allo-HSCT recipients conducted among the GITMO transplantation centers during the period of 2008 to 2010. It is intended as a guide for the identification of types and phases of transplantation at low, standard, and high risk for IFD, according to the underlying disease, transplantation, and post-transplantation factors. The risk stratification was the critical determinant of the primary antifungal approach for allo-HSCT recipients.

INTRODUCTION

In 2009, an expert panel (EP), representative of the Gruppo Italiano Trapianto Midollo Osseo (GITMO), published the results of a consensus process on the prophylaxis and therapy of invasive fungal diseases (IFD) in allogeneic hematopoietic stem cell transplantation (allo-HSCT) to improve awareness,

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diagnosis, and management of IFD, and to better define the current prophylactic and therapeutic options in the clinical practice [1]. Important issues considered in the consensus process were the definition of the risk level for IFD in different transplantation settings and different transplantation phases as critical determinants in the antifungal prophylaxis approach to allo-HSCT recipients. As the vulnerability of allo-HSCT recipients to IFD is multifactorial, no single risk stratification system can be identified. However, the EP agreed that an operational distinction could be made between standard and high-risk conditions for IFD, mainly invasive aspergillosis, during and after the engraftment phase. The consequence of this dichotomous classification was the indication or the lack of indication for the use of a mold-active primary antifungal prophylaxis (PAP) during and after the engraftment period. In addition, in these GITMO recommendations, the definition of patients at high risk for IFD, for whom a mold-active PAP would be recommended, was based on limited literature evidence, mainly derived from local experience, and was difficult to apply in clinical practice.

Over a period of 3 years (2008 to 2010), GITMO conducted a large, prospective epidemiological study involving 30 Italian transplantation centers to assess the current incidence, risk, and prognostic factors of IFDs in allo-HSCT recipients [2]. In a real-life scenario representative of the current allo-HSCT practice, this study was able to identify specific transplantation settings with a different risk of IFD during the pre-engraftment and postengraftment phases. Based on these original epidemiological GITMO data and on recent literature evidence, a new Consensus Development Conference Project was convened by GITMO with the aim to revise and update recommendations on PAP in patients undergoing allo-HSCT.

DESIGN AND METHODS

The EP included 19 individuals selected in view of their expertise in research and clinical practice of allo-HSCT. An advisory committee chaired by 4 clinicians (G.B., C.G., F.C., and A.R.) and a statistician (A.P.) with expertise in clinical epidemiology assured the proper methodology of the process. Of the 19 panelists, 11 had been involved in the previous GITMO epidemiological study.

The goal of the project was to develop recommendations for PAP of IFD in allo-HSCT. The areas of major concern in the PAP of IFD in allo-HSCT were selected by generating clinical key questions using the criterion of clinical relevance, ie, the impact on the management of patients and risk of inappropriateness, through a Delphi process [3].

Before the first meeting, the advisory committee examined the current state of knowledge regarding PAP of IFD in allo-HSCT, identified key questions, and drafted statements to address those questions. A systematic review of the literature on the epidemiology and PAP of IFDs in allo-HSCT populations (using the terms “epidemiology”, “fungal infections,” “allogeneic stem cell transplant,” and “antifungal prophylaxis” for the search) was performed on PubMed database, limiting the choice to English-language articles. Only articles including large single-center or multicenter series of allo-HSCT patients were considered. Based on the reviewed literature and on the results of the GITMO survey, the advisory committee formulated some recommendations. In detail, the conditions that proved to be significant risk factors for IFD in the different phases after transplantation represented the criteria for an evidence-based definition of PAP strategy; other expertise-based recommendations were proposed when relevant areas could not be addressed on the basis of the available evidence but when indirect evidence could support a statement. The literature review and the drafted statements were circulated by electronic mail to the EP members. With a 3-month interval, 2 meetings were held by the EP group in 2013: each panelist scored his/her agreement with the statements made by the advisory committee and the other panelists and provided suggestions for rephrasing. The ensuing comments were centrally combined for a subsequent round of electronic consultation, and agreement on the statements and the full body of recommendations were definitively approved.

The overall goal of the meetings was to reach a definite consensus over question-specific statements for which there was disagreement during the first-round postal phase. The nominal group technique [4] was used, through which participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote. If an 80% consensus on the statement was not achieved, the choices were discussed and a second vote taken. If an 80% consensus was still not attained, the issue was declared unresolved and no further attempt was made. The EP used a systematic weighting of the level and grade of the evidence for making a recommendation (Table 1) [5].

RESULTS

The key questions that were considered relevant for the present recommendations are the risk stratification and the choice of drugs for PAP.

Definition of Risk for Invasive Fungal Disease

The level of risk for IFD in allo-HSCT recipients depends on several factors, including host characteristics, underlying hematological disease conditions, type of transplantation, and post-transplantation complications. Risk may vary in different patients and also in the same patient at different times along the transplantation course [2,6-15]. Historically, neutropenia and acute and chronic graft-versus-host-disease (a-GVHD and c-GVHD) represent the major risk factors for infections during both the engraftment and post-engraftment phases. In epidemiological studies on populations who underwent transplantation in the previous decades, the vast majority of IFDs were documented late after engraftment and were generally associated with occurrence of GVHD [8,14,15]. In the more recent GITMO survey, more than one half of cases of IFD, mainly invasive aspergillosis, occurred during the early period and were generally associated with pre-engraftment length and deepness of neutropenia [2]. The high rate of IFD documented in this early phase after transplantation was related to the high number of patients who had 1 or more conditions associated with a significantly increased risk of early IFD. These risk factors included an IFD during the 6 months before transplantation, active acute leukemia at the time of transplantation, unrelated cord blood (CB), or unrelated volunteer donor (UD) graft: the incidence of early IFDs for patients with these risk factors was respectively 16%, 12%, 12%, and 6.4%. The high risk of reactivation early after allo-HSCT is well known in patients with a history of invasive aspergillosis before transplantation, and, in these patients, secondary prophylaxis is strongly recommended [16]. The high risk for the development of early IFDs in CB transplant

Table 1
Strength of Recommendation and Quality of Evidence

Category/ Grade	Definition
Strength of Recommendation	
A	Good evidence to support a recommendation for or against use.
B	Moderate evidence to support a recommendation for or against use.
C	Poor evidence to support a recommendation.
Quality of Evidence	
I	Evidence from $\geq$ 1 properly randomized, controlled trial.
II	Evidence from $\geq$ 1 well-designed clinical trial, without randomization; from cohort or case controlled analytic studies (preferably from $>$ 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Data from Freifeld AG, Bow EJ, Sepkowitz KA, et al [5].

recipients has been reported in several studies and it is due to several reasons, including delayed engraftment and naiveté of donor T cells (Table 2) [17-23]. The observation of a high rate of early IFDs in patients with active acute leukemia at the time of transplantation represents an original finding of the GITMO survey. Severe immunologic impairment associated with active disease, multiple intensive chemotherapy treatments, and late engraftment, frequently seen in these patients, justifies the high early post-transplantation risk of IFD [24-26].

GVHD (see standard criteria for diagnosis and staging [27]) represents a well-known risk factor for IFD in allo-HSCT. However, GVHD is a heterogeneous syndrome, which may significantly differ according to stem cell source, type of donor, and type of GVHD prophylaxis, with a consequent variable risk of IFD. The increased incidence of IFD in patients with grade III and IV a-GVHD, as compared with those with grade II, observed in the GITMO study confirms previous evidence of a correlation between GVHD severity, intensity of immunosuppressive therapy, and risk of IFD [8]. Donor type and the dynamic evolution of GVHD seem to be determinant factors affecting the infectious risk. The GITMO study showed that the risk for IFD in patients with grade II to IV a-GVHD not followed by extensive c-GVHD was low in patients who underwent transplantation from a matched related donor (MRD) (2.3%) and high in those who underwent transplantation from an alternative donor (mismatched related donor [MMRD], UD, and CB) (10%). When a-GVHD was followed by c-GVHD, the risk was high in either transplantations from MRD (10%) or, particularly, from alternative donors (25%). Of interest, the rate of IFDs in patients with c-GVHD not preceded by a-GVHD (also called *de novo* GVHD) was relatively low ($< 4\%$) in all types of transplantation.

These data suggest the possibility of stratifying the infectious risk in patients with GVHD, taking into account the transplantation setting and clinical presentation of GVHD.

Another population considered at high risk of infection is represented by patients undergoing transplantation from haploidentical donor, particularly when the graft is T cell depleted and is not followed by adoptive transfer of antigen-specific cells [28-35]. However, data from the literature are controversial and the rate of IFD seems to be variable in relation with the type of T cell depletion and of immunosuppressive regimen (Table 2).

With regard to the intensity of the conditioning regimen, a reduced risk of early IFD may be hypothesized in patients receiving a nonmyeloablative or reduced-intensity transplantation. However, both literature evidence and the GITMO survey, in particular, do not demonstrate any significant difference in the risk of IFD during the various phases after transplantation to suggest a tailored PAP strategy based on the intensity of the conditioning regimen [2].

Iron overload has been associated with increased risk of IFD in hematologic patients, and in allo-HSCT recipients, it has been shown to be correlated with pulmonary mold infection, mainly during the first 30 days from transplantation [10,36-38].

The EP agreed that 3 time periods should be distinguished in allo-HSCT: an early phase (from day 1 to 40), a late phase (from day 41 to 100), and a very late phase (after day 100) [8,12]. The 3 phases reflect the risk of IFD being associated with neutropenia (early), with a-GVHD and the early immune recovery (late), and with late a-GVHD or c-GVHD, together with late immunologic recovery (very late).

The EP agreed that patients could be stratified according to the need of a PAP strategy in 3 groups: those not requiring PAP (low-risk), those requiring a Candida-active PAP (standard risk), and those requiring a mold-active PAP (high risk). During the early and late post-transplantation phase, the GITMO data suggest that patients should be classified either at standard or high risk of IFD, with no patient qualifying for low risk. During the very late post-transplantation phase, patients may be classified at low, standard, and high risk of IFD.

Table 2
Characteristics and Risk for Invasive Fungal Disease in Cord Blood and Haploidentical allo-HSCT Studies

Author, Year	Type of Transplantation, Population (n)	Primary Antifungal Prophylaxis	Incidence of IFDs Overall/Early Phase, (%)
Cord blood allo-HSCT			
Saavedra, 2002 [17]	Single, adults (27)	Fluconazole plus aerosolized AmB	11/7.4
Parody, 2006 [18]	Single (48)	Fluconazole	23/10
Miyacoshi, 2007 [20]	Reduced-intensity conditioning, adults (128)	Fluconazole or micafungin	10.9/10.2
Cahu, 2009 [21]	Single (4) or double (27), adults	Fluconazole	10/10
Sauter, 2011 [22]	Double, without ATG (72)	Mica during conditioning followed by vori or posa	18/14
Ruggeri, 2011 [23]	Double, children and adults (35)	Fluconazole	34/12
GITMO study [2]	Not reported, children and adults (179)	Not reported	17.3/11.9
Haploidentical allo-HSCT			
Huang, 2006 [28]	Unmanipulated, children and adults (171)	Fluconazole	5.2/NR Most of IFD late or very late
Rizzieri, 2007 [29]	Unmanipulated, G-CSF primed PB transplantation, adults (49)	Not reported	8.2/NR
Huang, 2009 [30]	Unmanipulated, children (50)	Fluconazole	2/NR Only 1 IFD
Dodero, 2009 [31]	Ex vivo and in vivo T cell depleted, RIC, CD8-depleted DLI (28)	Itraconazole	10.7/NR Only 1 case of aspergillosis
Federmann, 2012 [32]	CD3/CD19 depleted, adults (61)	Not reported	NR. Only 2 very late deaths due to IFD
Sun, 2012 [33]	Unmanipulated, adults and children (291)	Fluconazole	13.4/7.9
Raiola, 2013 [34]	Unmanipulated, BM transplantation, adults (50)	Fluconazole	16/NR
Di Bartolomeo, 2013 [35]	Unmanipulated, G-CSF primed BM transplantation, adults (80)	Fluconazole	14/7
GITMO study [2]	Not reported, adults (72)	Not reported	8.2/5.4

Allo-HSCT indicates allogeneic hematopoietic stem cell transplantation; IFD, invasive fungal diseases; AmB, amphotericin B; ATG, antithymocyte globulin; G-CSF, granulocyte-colony stimulating factor; PB, peripheral blood; BM, bone marrow; RIC, reduced-intensity conditioning; DLI, donor lymphocyte infusion; NR, not reported; vori; voriconazole; posa, posaconazole.

Environmental precautions, in particular high efficiency particulate air filtration with positive pressure, proved to be of crucial importance in the prevention of airway filamentous fungi infections. Therefore, their use may condition the PAP strategy during the in-hospital stay of the patients. According to the recent epidemiological findings (most centers that participated in the GITMO survey were equipped with air filtration systems), the use of these measures was associated with a low rate of hospital-acquired mold infections in standard-risk patients who, therefore, require only a Candida-active PAP. By contrast, air filtration systems may be insufficient in high-risk patients.

Recommendations

1. In the early phase after allo-HSCT, for patients to be defined at high risk of IFD, thus requiring a mold-active PAP, they should have at least 1 of the following risk factors:
   a. acute leukemia with active disease at the time of transplantation (AII),
   b. CB transplantation (AII),
   c. grade III or IV a-GVHD after any type of transplantation (AII),
   d. MMRD or UD with 1 or more of the following additional risk factors: grade II a-GVHD, a steroid dose $\geq$ 2 mg/kg/day for at least 1 week, cytomegalovirus (CMV) disease, recurrent CMV infection, prolonged neutropenia (polymorphonuclear neutrophil $<$500/μL for more than 3 weeks), or iron overload (BIII),
   e. steroid refractory/dependent a-GVHD after any type of transplantation, defined as no response after 7 days of corticosteroid treatment or clear progression after 5 days and recurrence of a-GVHD signs with tapering of the corticosteroid dose and need of a chronic steroid therapy [39] (AIII).
2. In the early phase after allo-HSCT, all remaining patients not included in the high-risk category (standard risk) require a Candida-active PAP (AI).
3. In the late phase after allo-HSCT, patients at high risk of IFD requiring a mold-active PAP should have at least 1 of the following risk factors:
   a. acute grade III or IV GVHD after any type of transplantation (AII),
   b. transplantation from MMRD or UD and 1 or more of the following additional risk factors: grade II a-GVHD, a steroid dose $\geq$ 2 mg/kg/day for at least 1 week, CMV disease, recurrent CMV infection, or recurrent neutropenia (polymorphonuclear neutrophil $<$500/μL for more than 1 week) (BIII),
   c. steroid refractory/dependent a-GVHD after any type of transplantation (see above definition) (AIII).
4. All remaining patients not included in the high-risk category (standard risk) require a Candida-active PAP (BI).
5. In the very late phase after allo-HSCT, patients at high risk of IFD requiring a mold-active PAP are those with:
   a. persistent or late-onset grade III or IV a-GVHD (AII),
   b. persistent or late-onset steroid refractory/dependent a-GVHD after any type of transplantation (AII),
   c. persistent or late-onset grade II a-GVHD in patients after transplantation from MMRD or UD (BIII),
   d. extensive c-GVHD when preceded by a-GVHD (AII).
7. In the very late phase after allo-HSCT, patients at standard risk for IFD requiring a Candida-active PAP are those with limited c-GVHD who receive steroid-free immunosuppression (in general, a calcineurin inhibitor) and those with de novo c-GVHD (BII).
8. In the very late phase after allo-HSCT, patients at low risk for IFD not requiring any PAP are those free of any type of GVHD and free of steroid therapy (AII).

PRIMARY ANTIFUNGAL PROPHYLAXIS

The 2009 GITMO Consensus Conference, in agreement with the international guidelines, recommended, with high level of evidence (AI), the use of fluconazole and posaconazole as PAP in allo-HSCT patients, at least during the first 75 days after transplantation and in patients with GVHD, respectively [1]. These recommendations were based on the results of large prospective multicenter trials that demonstrated a decrease in the rate of Candida infection and the overall survival benefit at long-term follow-up associated with the use of fluconazole as compared with placebo and the significant reduction of the incidence of IFDs, invasive aspergillosis, in particular, in patients with GVHD who received posaconazole as compared with those who received fluconazole [40,41].

Since the GITMO Consensus Conference published in 2009, only few studies on PAP in the allo-HSCT population have been published [42-51], and only 2 of them were prospective, randomized, multicenter trials [43,46] (Table 3).

In the double-blind trial comparing voriconazole (305 patients) with fluconazole (295 patients), no difference of 6-month fungal-free survival was observed, and in the voriconazole arm there were no statistically significant reductions in IFD and invasive aspergillosis. A post hoc subanalysis showed an increased risk of IFD and a poorer fungal-free survival in patients with acute myeloid leukemia. Voriconazole significantly reduced IFDs (8.5% versus 21%, $P = .04$) and improved fungal-free-survival (78% versus 61%, $P = .04$) in this population [43]. An open-label study compared the efficacy and safety of voriconazole (234 patients) versus itraconazole (255 patients) [46]. The success of prophylaxis was significantly higher with voriconazole than with itraconazole (48.7% versus 33.2%, $P < .01$) as a result of a better voriconazole tolerability, although there was no difference in the either the incidence of IFD or survival.

Second-generation triazoles, voriconazole and posaconazole, have some pharmacokinetic limitations related to possible drug-drug interactions, erratic absorption, and unusual toxicities associated with long-term use. These limitations should be considered, particularly in allo-HSCT patients, who frequently suffer of gastrointestinal diseases and receive several other treatments, such as immunosuppressants, anticonvulsants, and other antimicrobial agents, which may interact with other drugs, with possible reciprocal modification in the pharmacokinetic and additive toxicity [52]. Drug-drug interaction and metabolic variability with the risk of either subtherapeutic levels or toxicity related to high blood levels has been frequently reported for voriconazole, whereas the reduced absorption of posaconazole in patients with mucositis or GVHD of the gastrointestinal tract may determine subtherapeutic concentrations with consequent suboptimal efficacy [53]. The evidence in the pharmacokinetic profiles of both voriconazole and posaconazole support the utility of monitoring blood concentrations (therapeutic drug monitoring [TDM]) of the drugs to ensure optimal systemic exposure [53,54].

Table 3
Main Results of the Studies of Primary Antifungal Prophylaxis in allo-HSCT Patients Published Since 2009

Author, Year	Type of Study, Drugs, No. of Patients	Results
Martin, 2010 [42]	Retrospective, single center. Voriconazole, from day -2 until immunosuppression, (n = 72).	In the first 120 days after transplantation, only 2 patients developed IFD. Only 14% of the patients required interruption of prophylaxis because of toxicity.
Wingard, 2010 [43]	Prospective, randomized, double-blind, multicenter. Voriconazole (n = 305) versus fluconazole (n = 295) for 100 days, or for 180 days in higher-risk patients.	Despite trends to fewer IFDs (7.3% versus 11.2%, $P = .12$), Aspergillus infections (9 versus 17, $P = .09$), and less frequent empiric antifungal therapy (24.1% versus 30.2%, $P = .11$) with voriconazole, fungal-free survival rates (75% versus 78%, $P = .49$) at 180 days were similar with fluconazole and voriconazole, respectively. Relapse-free and overall survival and the incidence of severe adverse events were also similar.
Morello, 2011 [44]	Retrospective, single center. AmB deoxycholate inhalation for a median duration of 16 days in addition to systemic prophylaxis (n = 102).	In 16 patients in whom aero-d-AmB was delivered for < 8 days, because of worsened clinical conditions or poor compliance, proven or probable airway mold infections were diagnosed in 3 cases, whereas in 84 patients receiving aero-d-AmB for > 8 days, 1 possible and 1 probable aspergillosis were diagnosed. At multivariate analysis, prolonged aero-d-AmB administration retained an independent protective effect on airways IFDs ($P = .026$)
Winston, 2011 [45]	Retrospective, single center. Posaconazole, day 1 to 100, or more, from transplantation (n = 106)	Breakthrough IFD on posaconazole occurred in 8 patients (7.5%) within 6 months after SCT; 3 additional patients developed IFD after discontinuation of prophylactic posaconazole. Mortality from IFD occurred in 4 patients (3.7%). Except for nausea in 9 patients, no clinical adverse event or laboratory abnormality could be attributed to posaconazole. Mean peak and trough plasma posaconazole concentrations were relatively low (400 ng/mL) in neutropenic patients with oral mucositis and other factors possibly affecting optimal absorption of posaconazole.
Marks 2011 [46]	Prospective, randomized, open label, multicenter. Voriconazole (n = 234) versus itraconazole (n = 255) for 100 days, or for 180 days in higher-risk patients.	Success of prophylaxis was significantly higher with voriconazole than itraconazole (48.7% versus 33.2%, $P < .01$). More voriconazole patients tolerated prophylaxis for 100 days (53.6% versus 39.0%, $P < .01$). There was no difference in incidence of proven/probable IFD (1.3% versus 2.1%) or survival to day 180 (81.9% versus 80.9%) for voriconazole and itraconazole, respectively.
Nihtinen, 2012 [47]	Retrospective, single center in patients with acute GVHD. AmB deoxycholate inhalation for a median duration of 84 days (n= 354) versus historical control (n = 257). No systemic prophylaxis.	Invasive aspergillosis was documented in 2.5% of patients versus 6.6% of controls. The median time to the diagnosis of invasive aspergillosis was155 days and 95 days from transplantation, respectively ($P = .2$). No discontinuation of prophylaxis because of side effects was recorded.
Molina, 2012 [48]	Prospective pilot study, single center, in children. Voriconazole (n = 56)	66.1% of patients successfully completed treatment (85.7% during neutropenic period) without empirical or preemptive antifungal therapy, adverse effects, or IFD. One (1.8%) probable IFD. A total of 10 (17.8%) children developed adverse effects related to voriconazole prophylaxis, leading to definitive withdrawal.
Doring, 2012 [49]	Retrospective, single center in children. L-amB (n = 60) versus caspofungin (n = 60) from day 0 until hospitalization.	No proven breakthrough fungal infection occurred in either group during the median treatment period of 23 days in the L-AmB group and 24 days in the caspofungin group. One patient receiving caspofungin developed probable invasive aspergillosis. Patients treated with L-AmB had more drug-related side effects and an increased need for oral supplementation with potassium, sodium bicarbonate, and calcium upon discharge as compared with the caspofungin group. Caspofungin was well tolerated and safe.
Doring, 2012 [50]	Retrospective, single center in patients under 12 years of age. L-amB or caspofungin during hospitalization, posaconazole at discharge until day 100, or more, from transplantation (n= 60).	No proven or probable IFD was documented during treatment with posaconazole as antifungal prophylaxis. No severe side effects.
El-Cheikh, 2013 [51]	Retrospective, single center, haploidentical transplantation. Micafungin, from conditioning until hospital discharge (n =26).	No IFD at 6 months from transplantation. No patient discontinued the treatment for drug-related adverse events.

Allo-HSCT indicates allogeneic hematopoietic stem cell transplantation; IFD, invasive fungal disease; aero-d-AmB, amphotericin B deoxycholate inhalation; GVHD, graft-versus-host disease; L-amB, liposomal amphotericin B.

Recommendations

1. Fluconazole (400 mg/day in adults and 8 to 12 mg/kg/day in children, administered intravenously or orally) is the drug of choice for a Candida-active PAP in any phase after transplantation in patients at standard risk for IFDs (AI). It should be continued at least until day 75 from transplantation or until immunosuppressive

Table 4
Recommendations for Primary Antifungal Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplantation Patients

Level of Risk for IFD	Criteria for the Definition of the Level of Risk			PAP Recommended
	Early Phase after Transplantation (Day 0-40)	Late Phase after Transplantation (Day 41-100)	Very Late Phase after Transplantation (Day > 100)	
High risk	• Active acute leukemia at the time of transplantation (AII), • CB transplantation (AII), • Grade III-IV a-GVHD after any type of transplantation (AII), • Transplantation from MMRD or UD and 1 or more of the following additional risk factors: grade II a-GVHD, steroid dose $\geq$ 2 mg/kg/day for at least 1 week, CMV disease, recurrent CMV infection, prolonged neutropenia (PMN $<$ 500/μL for more than 3 weeks), iron overload (BIII), • Steroid refractory/dependent a-GVHD after any type of transplantation (AIII).	• Acute grade III-IV GVHD after any type of transplantation (AII), • Transplantation from MMRD or UD and 1 or more of the following additional risk factors: grade II a-GVHD, steroid dose $\geq$ 2 mg/kg/day for at least 1 week, CMV disease, recurrent CMV infection, recurrent neutropenia (PMN $<$ 500/μL for more that 1 week) (BIII), • Steroid refractory/dependent a-GVHD after any type of transplantation (AIII).	• Persistent or late-onset grade III-IV a-GVHD (AII), • Persistent or late-onset steroid refractory/dependent a-GVHD after any type of transplantation (AII), • Persistent or late-onset grade II a-GVHD after transplantation from MMRD or UD (BIII), • Extensive c-GVHD when preceded by an a-GVHD (AII).	Mold-active PAP is recommended. • Posaconazole in GVHD (AI) (TDM advised for oral solution) • Voriconazole (BI) (TDM advised) • Liposomal Amphotericin B (CIII) • Caspofungin (CIII) • Micafungin (CIII) • Aerosolized amphotericin B plus fluconazole (CIII)
Standard risk	All remaining patients not included in the high-risk category (AI).	All remaining patients not included in the high-risk category (BII).	Limited c-GVHD in patients who receive only a nonsteroid immunosuppression and "de novo" c-GVHD (BIII).	Candida active PAP is recommended. Fluconazole (AI) Voriconazole (BI) Itraconazole(BI) Micafungin (BI)
Low risk	No patient may be considered at low risk for IFD during this phase.	No patient may be considered at low risk for IFD during this phase.	Absence of any type of GVHD and no steroid therapy (AII).	No PAP is recommended

PAP indicates primary antifungal prophylaxis; CB, cord blood; MMRD, mismatched related donor; UD, unrelated donor; a-GVHD, acute graft-versus-host disease; c-GVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; TDM, therapeutic drug monitoring; IFD, invasive fungal disease; PMN, polymorphonuclear neutrophil.

therapy is discontinued (BIII). Fluconazole should be replaced with a mold-active drug if high-risk conditions for IFD occur. Itraconazole, micafungin, and voriconazole proved to be as effective as fluconazole in the prophylaxis of Candida infections during the engraftment phase in large controlled trials [43,55,56]; furthermore, micafungin is active on triazole-resistant Candida strains and lacks clinically relevant drug-drug interaction. Although these drugs may be considered an alternative to PAP during the early phase after transplantation in standard-risk patients, fluconazole should be preferred, considering the advantages in cost (compared with micafungin and voriconazole) and tolerability (compared with itraconazole and voriconazole). In view of these considerations, the EP agreed on a moderate recommendation for the use of these drugs for the prevention of Candida infections (BI).

2. A mold-active PAP should be used in high-risk patients in any phase after transplantation. The evidence of efficacy, different pharmacokinetic, drug-drug interaction, and toxicity profile of the various antifungal drugs should be considered in the choice of PAP in each single patient [52]. Posaconazole oral solution (600 mg/day in adults or 12 mg/kg/day in children) is the drug of choice for patients with GVHD at high risk for IFD (AI). This formulation of posaconazole has the potential limitation of erratic absorption, especially in patients with intestinal GVHD and/or diarrhea. Therefore, TDM is recommended in such conditions. The upcoming availability of posaconazole tablets with an improved absorption and no need for TDM will probably extend the use of this triazole in PAP [57]. In consideration of the results of the above-mentioned controlled studies, in which voriconazole showed some advantages compared with fluconazole and itraconazole, there is moderate evidence for the use of voriconazole as PAP in high-risk allo-HSCT recipients as an alternative to posaconazole, particularly in the early phase after transplantation (BI). Voriconazole may be preferred to posaconazole in patients with impaired absorption (ie, in patients with GVHD involving the gastrointestinal tract), a condition potentially limiting the use of posaconazole. It should be also considered that inter- and intrapatient metabolic variability is a major concern in voriconazole treatment and TDM is recommended, especially in the pediatric population [58]. The few retrospective experiences on the use of aerosolized amphotericin B in association with fluconazole, of liposomal amphotericin B, and of the echinocandins caspofungin and micafungin do not allow any recommendation for the use of these drugs as PAP in high-risk patients (CIII). Mold-active PAP should be continued until discontinuation of steroid and any other immunosuppressive therapy (BIII).

CONCLUSIONS

Most of trials of PAP in allo-HSCT have been performed in populations with risk of developing IFD and results obtained in these studies may be difficult to apply in the different types and phases of transplantation. As a consequence, most clinical decisions continue to derive from personal experience and subjective considerations [5,59,60]. The definition of the level of risk for IFD associated with the various types and phases of transplantation is the critical determinant of any prevention strategy and represents the first step of a decision-making PAP algorithm (Table 4). Considering the difficulty in performing adequate interventional trials in subpopulations of allo-HSCT patients, most of the information for planning tailored prevention strategies in clinical practice must be drawn from large epidemiological, possibly prospective studies and the recent GITMO survey provides a useful estimate of the current levels of infectious risk for IFDs in the various transplantation subpopulations [2]. In the present report, experts in the field judged whether the body of evidence from this GITMO study and recent literature was sufficient to provide information for the definition of new recommendations for PAP in allo-HSCT recipients. The questions raised by and the conclusions drawn from this consensus conference project may form the basis for improving efforts in the prevention of IFDs in the allo-HSCT populations.

Current evidence from the literature is not able to give comprehensive information on all clinical issues of the allo-HSCT procedure; consequently, the present recommendations may be insufficient to meet many clinical needs. A continuous epidemiological update is needed to implement the guidelines to be applied in the clinical practice.

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