Prophylaxis and Treatment of Invasive Fungal Diseases in Allogeneic Stem Cell Transplantation: Results of a Consensus Process by Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

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In recent years, prospective studies have been conducted to assess the role of prophylaxis and treatment of invasive fungal diseases (IFD) in allogeneic hematopoietic stem cell transplantation (allo-HSCT). Although results of these studies have been encouraging, they have been unable to generate a consensus for optimal management of IFD in the complex scenario of allo-HSCT. A consensus process was undertaken to describe and evaluate current information and practice regarding key questions on IFD management in allo-HSCT recipients; these questions were selected according to the criterion of relevance by group discussion. The Panel produced recommendations for risk stratification, prophylaxis, monitoring, and therapy of IFD and identified top priority issues for further investigation. The definition of the level of risk for IFD associated with the various types and phases of transplantation and the implementation of surveillance and diagnostic strategies are the critical determinants of the antifungal prophylactic and therapeutic approach for allo-HSCT recipients.

Invasive fungal diseases (IFDs) represent a leading cause of morbidity and mortality among allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients [1–11]. A cohort-retrospective study, conducted during the period 1999–2003 at 11 Italian transplantation centers showed a 7.8% incidence (98 patients) of proven or probable invasive fungal infection among 1249 allo-HSCT recipients, with an attributable mortality rate of 72.4% [12]. Aspergillosis accounted for 80% of microbiologically documented infections. This study provides an additional piece of evidence supporting the increasing impact of severe mold infections on the outcome of patients who receive allo-HSCT.

In the past few years, several new antifungal agents have become available, and several prospective studies have been conducted to assess the role of prophylaxis and treatment of IFD in allo-HSCT. Although results of some of these studies were encouraging, taken altogether, they have been unable to generate a consensus for optimal management of IFD in the complex scenario of allo-HSCT.

To improve awareness, diagnosis, and management of IFD in allo-HSCT and to better define the current prophylactic and therapeutic options in clinical practice, a Consensus Development Conference Project was convened. The conclusions of the project were endorsed by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO).

DESIGN AND METHODS

Organization. An Expert Panel that included 13 experts was selected on the basis of expertise in research and clinical practice of allo-HSCT. An Advisory Commit-
Framing the domain of recommendations. The Expert Panel agreed on the goal of developing recommendations for prophylaxis against and therapy of IFD in allo-HSCT and generated clinical key questions using the criterion of clinical relevance through a Delphi process [13]. The key questions that were considered to be relevant formed the set of questions for the present recommendations.

The consensus process. During the first meeting, each panelist drafted statements that addressed 1 of the preliminarily identified key questions. Subsequently, each panelist scored his or her agreement with the statements made by the other panelists and provided suggestions for rephrasing. To conduct this process, the Expert Panel was convened, and 3 consensus meetings were held in Milan, Italy. The overall goals of the meetings were to reach a definite consensus regarding those question-specific statements for which there was disagreement during the first-round postal phase. The nominal group technique [14], by which participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote, was used. If an 80% consensus on the statement was not achieved, the choices were discussed, and a second vote was taken. If an 80% consensus was still not attained, the issue was declared undecidable, and no further attempt was made.

The Expert Panel took note of the recommendations already given by the Infectious Diseases Society of America (IDSA) Guidelines on the basis of evidence from the literature and rated them according to the IDSA standard scoring system [15–17]. The recommendations that were not clearly supported by literature evidence but were derived from the present consensus process were not rated and were identified as being the result of the Expert Panel opinion (EPO).

RESULTS

The key questions that were considered to be relevant for the present recommendations are the following: risk stratification, prophylaxis, monitoring of patients under prophylaxis, therapy, and research issues.

Risk stratification

Factors that contribute to risk for IFD are summarized in Table 1 [2–11]. Although neutropenia was historically the major risk factor for IFD, recent studies have demonstrated a reduction in the incidence of neutropenia-related infection and an increase in that of late infection occurring in concomitance with graft versus host disease (GvHD) and reactivation of cytomegalovirus (CMV) infection [11]. Particular settings in which there is an elevated risk for IFD include cord blood transplant (CBT) or T cell-depleted HSCT from a human leukocyte antigen (HLA)—haploidentical donor: in these settings, the lack of adoptive transfer of antigen-experienced cells, together with delayed neutrophil engraftment occurring in CBT recipients, favor the development of IFD in the early posttransplantation period [4–9].

The Expert Panel discussed stratification of patients according to the risk for IFD associated with different transplant settings and phases, with the aim of planning specific prevention and treatment strategies.

Recommendations

1. The vulnerability of allo-HSCT recipients to IFD is multifactorial, and it is not possible to assess a per-
percentage range of risk associated with each risk factor. However, an operational distinction could be made between standard conditions and conditions that involve a high risk for IFDs (mainly those IFDs caused by molds) (EPO). The consequence of this dichotomous classification is the indication or the lack of indication for a prevention strategy with a mold-active drug. The risk condition should be defined at the time of transplantation but may be upgraded or downgraded after the allograft is received.

2. At the time of allo-HSCT, the criteria that singularly may identify patients at high risk for IFD are as follows: (1) IFD before receipt of transplant, particularly those caused by mold, and (2) CBT or HSCT from an HLA-haploidentical family donor (EPO). There are other risk factors that may, when combined together, identify patients who are at high risk for developing IFD (Table 1). The resulting risk stratification should be defined for each patient.

3. After allo-HSCT, the criteria that singularly may identify patients at high risk for IFD are as follows: (1) severe acute or extensive chronic GvHD, (2) prolonged (ie, >3 weeks duration) or recurrent severe neutropenia (<0.5×10^9 polymorphonuclear neutrophils/L) (3) receipt of steroids ≥2 mg/kg/day for at least 1 week, and (4) recurrent CMV infection requiring ganciclovir therapy (EPO).

### Prophylaxis

Prevention strategies for IFD in allo-HSCT recipients are based on environmental precautions and antimicrobial prophylaxis. Although there is general agreement with respect to the environmental precautions, the role of pharmacological prophylaxis is still debated [18].

Fluconazole (400 mg/daily for adults and 6 mg/kg for children) has been recommended for primary prophylaxis against *Candida* infection starting from the initiation of the conditioning regimen. The time at which to discontinue fluconazole, however, is more controversial [19–21]. This prophylactic strategy proved to decrease the rate of *Candida* infection and was associated with an overall survival benefit at long-term follow-up [21]. However, a major limitation of fluconazole prophylaxis is the lack of activity against molds.

In the past few years, several broad-spectrum antifungal drugs have been randomly compared with standard fluconazole for the prophylaxis of IFD in allo-HSCT recipients, with the aim of determining a prophylactic regimen that would also prevent mold infections. Two trials compared intravenous and oral fluconazole with low-dose intravenous amphotericin B (AmB) deoxycholate (administered at a dosage of 0.2 mg/kg once daily or 0.5 mg/kg 3 times per week) [22, 23]. There was no difference with respect to all-cause mortality, fungal-related mortality, and any occurrence of IFD, but fluconazole was significantly better tolerated. No lipid formulation of AmB (LFAmB) has been randomly compared with fluconazole in the prophylaxis of IFD in allo-HSCT. In a recent placebo-controlled trial, inhalation of liposomal AmB (LipAmB) reduced the incidence of pulmonary aspergillosis among neutropenic patients [24]. However, few allo-HSCT patients were included in this study, and no conclusion can be drawn for this population.

Two trials compared the efficacy of intravenous and oral itraconazole with that of intravenous and oral fluconazole in allo-HSCT [25, 26]. Patients who received itraconazole had fewer IFDs caused by *Candida glabrata*, *Candida krusei*, and *Aspergillus* species, although there was no difference in overall or fungal-free survival. Both drugs were well tolerated, but oral itraconazole was associated with treatment discontinuation because of toxicities or gastrointestinal intolerance.

The echinocandin micafungin (50 mg/day) was compared with fluconazole (400 mg/day) in a double-blind, multicenter trial as prophylaxis against IFD during the pre-engraftment phase [27]. Both drugs were effective for preventing candidiasis, and there was a trend towards the reduction of aspergillosis in favor of patients who received micafungin. The echinocandin was associated with fewer withdrawals from the study due to adverse events.

In a multicenter, double-blind trial involving patients with GvHD, oral posaconazole (600 mg/day) significantly reduced the incidence of IFD and of breakthrough *Aspergillus* infections, compared with fluconazole [28]. However, there was no difference with respect to all-cause mortality. There was no difference in the prevalence of adverse reactions causing discontinuation of the study drug.

A randomized, double-blind trial of fluconazole versus voriconazole for the prevention of IFD in allo-HSCT showed similar cumulative rates of IFD in the 2 arms (10.6% for fluconazole and 6.6% for voriconazole), although *Aspergillus* infections were significantly less common among patients who received voriconazole (2.2% vs 5.4%; *P* = .05). Event-free and overall survival rates were similar in both arms [29].

On the basis of the above studies, international guidelines recommend the use of fluconazole during the engraftment phase and posaconazole during intensive immunosuppressive therapy for GvHD [16, 30]. These key recommendations imply 2 major problems: (1) the lack of any approved mold-active prophylaxis during the engraftment phase, and (2) the lack of an intravenous formulation of posaconazole that could limit its use in patients who are unable to tolerate oral medications, as well as when oral and intestinal mucositis and...
diarrhea occur, which would render the intestinal absorption of the drug erratic.

Occasionally, patients with a previous IFD are referred for an allo-HSCT. Recurrence or progression of an earlier IFD, predominantly due to molds, ranges from 10% to 33% following allo-HSCT, despite secondary antifungal prophylaxis [31–37]. Few data are available regarding the role of secondary prophylaxis with specific antifungal agents, preventative surgical resection of pulmonary lesions, and prophylactic granulocyte transfusions during neutropenia [32–37].

The Expert Panel discussed different transplant types and phases stratified according to their risk for IFD (standard or high) and thus the eligibility of patients for a primary prophylaxis with fluconazole or with a mold-active drug. Finally, the Expert Panel analyzed the role and indications of secondary antifungal prophylaxis.

**Recommendations**

**Primary prophylaxis**

1. Primary systemic antifungal prophylaxis is recommended for all allo-HSCT recipients and should start together with the conditioning regimen (AI); it should be maintained at least until sustained engraftment, but it is probably appropriate to prolong prophylaxis until day 75 in the absence of acute GVHD (EPO).

2. In patients with severe acute and/or extended chronic GVHD that requires immunosuppressive therapy (who are at high risk for IFD), antifungal prophylaxis should be given regardless of the time from receipt of transplant (AII).

3. In patients at standard risk for IFD in the early phases after transplant, fluconazole (400 mg/day administered intravenously or orally) is the drug of choice for primary prophylaxis (AI), and mold-active drugs are not indicated (EPO).

4. In patients who are at high risk for IFD in the early phases after receipt of the transplant (in particular, adult patients who received haploidentical transplant or CBT), intravenous mold-active antifungal drugs might be considered (EPO). Although intravenous itraconazole or an echinocandin may be used in this setting, LipAmB seems to be a more attractive option, considering its drug interaction profile, antimicrobial spectrum, and local experiences (EPO).

5. Posaconazole (600 mg/day orally) is the drug of choice for patients with GVHD that requires treatment (AI). It should be continued until presumed recovery of the immune status (BIII).

6. A potential limitation of posaconazole is erratic oral absorption, especially in patients with intestinal GVHD and/or diarrhea. In this setting, monitoring of drug levels should be considered (BII). Alternatively, other intravenous mold-active antifungal drugs should be considered (EPO).

**Secondary prophylaxis**

1. Patients with a history of mold infection or invasive candidiasis with organ involvement should receive secondary antifungal prophylaxis from the beginning of conditioning and during the period of severe neutropenia, during immunosuppressive therapy, and/or until immune reconstitution (AIII).

2. No particular antifungal drug can be recommended as secondary antifungal prophylaxis. The choice of the drug should take into account the pathogen responsible for the primary episode, the site of infection, pharmacological considerations, and drug-drug interactions (EPO).

**Monitoring of patients who receive antifungal prophylaxis**

Surveillance strategies should have a high positive predictive value for early detection of breakthrough IFD and a high negative predictive value for excluding IFD, thus avoiding unnecessary modifications in antifungal prophylaxis. Preemptive antifungal strategies based on predefined surveillance and diagnostic work-up with laboratory markers and radiological findings have been proposed [38–43]. Both serum *Aspergillus* galactomannan and panfungal β-glucan assays have been accepted as diagnostic adjuncts for IFD [44]. Galactomannan detection in samples other than serum could be a useful diagnostic tool, but its role has not been standardized to date. These markers have some limitations, such as low sensitivity of the assay to concomitant mold-active antifungal agents and a series of false-positive results, including those observed in patients with gastrointestinal GVHD [42, 45–47]. The Expert Panel discussed clinical and microbiological diagnostic schedules for the detection of IFD in patients with various types of transplant and at different phases of transplantation, aiming at the definition of strategy that would be feasible for transplant centers with standard diagnostic resources.

**Recommendations**

1. A surveillance strategy and/or an active diagnostic approach are recommended. Surveillance is a monitoring strategy for patients who are at high-risk but have no signs or symptoms suggestive of a diagnosis of IFD. An active diagnostic approach is defined as a strategy for patients with signs or symptoms of and/or microbiologic data possibly related to an IFD (EPO).

2. For patients who receive primary antifungal prophylaxis, the goal of a surveillance strategy is the early detection of a breakthrough IFD. During secondary prophylaxis, the goal of a surveillance strategy is the early detection of both the reactivation of the previous IFD and the development of a new IFD.

3. For patients at high risk for IFD, both surveillance and an active diagnostic approach are required. For patients with standard risk for IFD,
only an active diagnostic approach is recommended (EPO).

4. Surveillance is based on the serum detection of galactomannan or β-glucan antigen and on the detection of respiratory tract colonization by filamentous fungi (sputum and nasal swab samples) (EPO).

5. Fungal antigen assays should be performed at least twice per week for hospitalized patients and at least once per week for outpatients. The optical density index cutoff level for the galactomannan assay is 0.5, whereas the cutoff level for the β-glucan assay has not been clearly defined. Nasal swab samples should be obtained for culture once every other week, and sputum cultures should be performed when possible (EPO).

6. In the event of a single positive serum antigen assay result or a culture positive for molds during surveillance, an active diagnostic approach should be performed to confirm the presence of an asymptomatic IFD or, alternatively, to demonstrate a false-positive result (EPO).

7. For patients who are receiving secondary prophylaxis, surveillance should include the clinical, radiological, and microbiological monitoring of the previous IFD according to the single patient characteristics (EPO).

8. An active diagnostic approach may include serum fungal antigen detection and radiologic (ie, thoracic and sinonasal computed tomography scan) and microbiologic (ie, sputum, bronchoalveolar lavage fluid, blood, or other cultures) examinations according to the signs and symptoms possibly related to an IFD. Experiences published to date have considered the detection of fungal serum antigens only in the context of a surveillance strategy. However, an active diagnostic approach in patients with a suspected IFD may include strict antigen detection (eg, daily for 3 consecutive days) to improve the sensitivity of the test (EPO).

9. An active diagnostic approach should be performed in the event of fever unresponsive to antibacterial therapy and/or signs and symptoms possibly related to an IFD, as well as in asymptomatic patients at high risk who have test results positive for a fungal antigen (EPO).

Antifungal therapy

Empiric antifungal therapy has been widely employed for neutropenic patients, including allo-HSCT recipients. However, fever is a poorly predictive surrogate of IFD and this approach may result in needless, potentially toxic and costly antifungal treatments [48–55]. These arguments argue against considering fever alone as the indicator for a therapeutic decision and indicate preemptive strategies as an alternative option for patients with early markers suggestive for IFD, but still no evidence of disease [38–40, 43]. However, in spite of the implementation of antifungal strategies with drugs very active against both yeasts and molds and with a good safety profile, the prognosis of IFD in the allo-HSCT setting continues to be very poor, and the choice of the best antifungal treatment in any single patient remains a crucial problem in the clinical practice. Moreover, immune reconstitution inflammatory syndrome (IRIS) may occur in a subset of patients after allo-HSCT and can be diagnostically challenging. It may play an even greater role leading to a misdiagnosis of antifungal treatment failure.

Therapeutic options in microbiologically documented IFD have been well defined in international guidelines [16, 17]. On the contrary, the choice of the best drug for suspected IFD lacking an etiological confirmation, remains a matter of debate. In fact, the so called “broad spectrum antifungal drugs” present different spectrum of activity which may dramatically affect the efficacy of the treatment. The extremely poor outcome of patients with IFD has prompted the use of combination antifungal therapy; but we neither have data comparing combined versus single drug therapy, nor we know if a double or triple agent regimen should be used.

In view of the availability of recent international guidelines on the treatment of IFD, the Expert Panel focused its efforts on the discussion and definition of therapeutic strategies in the clinical practice more than the choice of antifungal drugs in well-documented infections.

Recommendations

Empirical and preemptive therapy

1. Empirical therapy may be administered to febrile, neutropenic patients without signs or symptoms specifically suggestive of an IFD but who do not respond to an apparently effective antibacterial therapy after a period of 4–7 days (BII). An empirical antifungal approach must follow a proper diagnostic effort and cannot be a remedy for an inadequate surveillance and diagnostic strategy.

2. LipAmB or caspofungin are the drugs of choice for empirical therapy (AI).

3. Preemptive therapy is a diagnostic-driven strategy. The choice of the antifungal drug derives from the level of etiological documentation and should be based on a consideration of the fungal pathogens that are possibly involved (EPO).

Therapy for aspergillosis

1. Voriconazole is the drug of first choice for probable and proven invasive aspergillosis (AI).

2. LipAmB can be a suitable alternative (AI).

3. AmB deoxicholate is no longer indicated because of renal toxicity and infusion reactions, which cause significant dose reduction or discontinuation (AI).

4. For salvage therapy, agents include LFAmB (AII), posaconazole (B-II), itraconazole (B-II), caspofungin (BII), or micafungin (BII). In these cir-
3. Fluconazole (12 mg/kg/day) can be used for patients who are not critically ill and who have had no recentazole exposure (AIII).
4. The identification of the Candida species is important for the choice of the drug. For infections due to C. glabrata, an echinocandin is preferred (BII). For infections due to C. krusei, an echinocandin, LFAmB, or voriconazole are recommended (BIII).
5. Candidemia without obvious metastatic complications requires treatment for at least 2 weeks after the last positive blood culture result is obtained, but invasive candidiasis may require treatment throughout the duration of residual immunosuppression (AIII).
6. Catheter removal is recommended whenever possible in every case of candidemia, especially for nonneutropenic patients and when venous line infection is suspected (AII).

Therapy for candidiasis
1. Most of the prospective controlled trials that demonstrated the efficacy of antifungal drugs in the treatment of candidemia and invasive candidiasis focused on nonneutropenic patients who had not received HSCT. Therefore, the strength of recommendations developed on the basis of the general population should be considered with caution when applied to allo-HSCT recipients.
2. An echinocandin (caspofungin [AII], micafungin [AII], or anidulafungin [AIII]) or LFAmB [AII] is recommended during neutropenia and for patients in critical conditions or with deep infection or when the species identification or susceptibility of the pathogen is unknown.
3. Fluconazole (12 mg/kg/day) can be used for patients who are not critically ill and who have had no recentazole exposure (AIII).
4. The identification of the Candida species is important for the choice of the drug. For infections due to C. glabrata, an echinocandin is preferred (BII). For infections due to C. krusei, an echinocandin, LFAmB, or voriconazole are recommended (BIII).
5. Candidemia without obvious metastatic complications requires treatment for at least 2 weeks after the last positive blood culture result is obtained, but invasive candidiasis may require treatment throughout the duration of residual immunosuppression (AIII).
6. Catheter removal is recommended whenever possible in every case of candidemia, especially for nonneutropenic patients and when venous line infection is suspected (AII).

Therapy for zygomycosis
1. Initial treatment should be performed using LipAmB (EPO). High dosages (≥5 mg/kg/day) may be required (EPO).
2. Posaconazole is suitable for long-term suppressive treatment because of its relatively low toxicity and because it can be administered orally (EPO).
3. The promising efficacy of the combinations AmB plus posaconazole and AmB plus caspofungin in treating zygomycosis has been recently reported [56–58] and merits further investigation (EPO).
4. Surgical intervention may be pivotal in treating sinonasal infections for clinical response and long-term survival (EPO).

Intracranial fungal infections
1. Neurosurgical resection of infected lesions may be an important adjunct to improve antifungal therapy when the risk-benefit ratio is favorable (AII). The risk-benefit quotient cannot be predefined but should be evaluated for each patient, taking into account a series of clinical aspects.
2. The recommended medical therapy for intracranial aspergillosis is voriconazole (AII). The combination of caspofungin and voriconazole has a possible synergic or additive antifungal activity and can be used (EPO).
3. The combination of high-dose LipAmB and voriconazole may be considered when the diagnosis is uncertain (EPO).
4. Anticonvulsivant agents that could interact with voriconazole should be avoided (CIII).
5. The use of steroid therapy is not recommended (CIII).

Interactions and blood levels
1. Drug level monitoring during prophylaxis with oral azoles should be considered. It is recommended for patients who receive itraconazole, might be useful for those who receive voriconazole, and is probably useful for those who receive posaconazole (BII). The target level for itraconazole is >0.5 μg/mL, although some authors propose a dosage of >0.5 μg/mL for prophylaxis and of >1 μg/mL for treatment. A voriconazole level of <2.0 μg/mL correlates with failure to respond to therapy, and ≥6 μg/mL correlates with neurological toxicity. For posaconazole, there is currently no accepted target drug concentration; however, some authors have proposed a through posaconazole goal of 0.5–1.5 μg/mL for therapy and ≥0.5 μg/mL for prophylaxis [59].
2. Drug-drug interaction may represent a problem that should be recognized and appropriately managed when using a triazole with other drugs that are metabolized within the P450 cytochrome system (Table 2). To a lesser extent, caspofungin and micafungin also have a potential to interact with some immunosuppressive drugs.
3. Although drug interactions must always be taken into consideration, the...
Table 2. Important Drug-Drug Interactions involving Antifungal Drugs in Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

<table>
<thead>
<tr>
<th>Drug, type of interaction</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td><strong>Fluconazole</strong></td>
<td></td>
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<tr>
<td>Levels increased by fluconazole</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine, tacrolimus</td>
<td>Monitor calcineurin drug levels</td>
</tr>
<tr>
<td>Decreased levels of fluconazole</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Monitor levels of fluconazole</td>
</tr>
<tr>
<td><strong>Itraconazole</strong></td>
<td></td>
</tr>
<tr>
<td>Levels increased by itraconazole</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Cyclosporine, tacrolimus</td>
<td>Monitor calcineurin drug levels</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Methylprednisolone and dexamethasone</td>
<td>Monitor steroids side effects and reduce dosages</td>
</tr>
<tr>
<td>Alprazolam, diazepam, temazepam, triazolam, midazolam</td>
<td>Consider switch to benzodiazepine not metabolized by cytochrome P3A4 (lorazepam)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Monitor digoxin levels</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Monitor international normalized ratio and adjust warfarin dose</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Although no significant adverse effects occur, clinician should be aware of any unexplained drowsiness or vomiting</td>
</tr>
<tr>
<td>Decreased levels of itraconazole</td>
<td></td>
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<tr>
<td>Carbamazepin</td>
<td>Monitor levels of itraconazole</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Monitor levels of itraconazole</td>
</tr>
<tr>
<td>Gastric pH modifiers</td>
<td>Monitor levels of itraconazole only with use of itraconazole capsules</td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td></td>
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<tr>
<td>Levels increased by voriconazole</td>
<td></td>
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<tr>
<td>Cyclophosphamide</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Reduce cyclosporine dosage by one-half and monitor levels</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Reduce dosage by one-half</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Reduce dosage to a third and monitor levels</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Monitor international normalized ratio and adjust warfarin dosage</td>
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<tr>
<td>Decreased levels of voriconazole</td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td>Double voriconazole dosage and monitor for increased phenytoin levels</td>
</tr>
<tr>
<td><strong>Posaconazole</strong></td>
<td></td>
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<tr>
<td>Levels increased by posaconazole</td>
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<tr>
<td>Cyclosporine</td>
<td>Monitor cyclosporine levels</td>
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<tr>
<td>Tacrolimus</td>
<td>Monitor tacrolimus levels</td>
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<tr>
<td>Decreased levels of posaconazole</td>
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<tr>
<td>Phenytoin</td>
<td>Consider increase posaconazole dosage and monitor for increased phenytoin levels</td>
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<tr>
<td><strong>Caspofungin</strong></td>
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<tr>
<td>May increase clearance of caspofungin</td>
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<tr>
<td>Rifampin, carbamazepine, dexamethasone, phenytoin</td>
<td>Consider increase in caspofungin dosage to 70 mg</td>
</tr>
<tr>
<td>Levels decreased by caspofungin</td>
<td></td>
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<tr>
<td>Tacrolimus</td>
<td>Monitor tacrolimus levels</td>
</tr>
<tr>
<td>Increased caspofungin levels</td>
<td></td>
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<tr>
<td>Cyclosporine</td>
<td>Monitor liver function tests</td>
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<tr>
<td><strong>Micafungin</strong></td>
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<tr>
<td>Levels increased by micafungin</td>
<td></td>
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<tr>
<td>Sirolimus</td>
<td>Monitor sirolimus levels</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Monitor clinically</td>
</tr>
<tr>
<td>Amphotericin B (interactions more frequent with conventional formulation than with liposomal formulation)</td>
<td></td>
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<tr>
<td>Increased risk of nephrotoxicity if concomitant use of other nephrotoxic drugs such as; cyclosporine, aminoglycosides, foscarnet.</td>
<td>Monitor creatinine levels and creatinine clearance</td>
</tr>
<tr>
<td>Increased risk of ipokaliemia if concomitant use of furosemide, amiodarone</td>
<td>Monitor potassium levels and consider supplementation</td>
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</tbody>
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**NOTE.** Only some of the drugs that are commonly used by HSCT recipients were considered, but important interactions with other drugs may occur.
Table 3. Prophylaxis and Treatment of Invasive Fungal Disease (IFD) in Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

<table>
<thead>
<tr>
<th>Key question</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk stratification</td>
<td>An operational distinction can be made between standard and high-risk conditions for IFD (mainly, those caused by molds). High-risk conditions may indicate a mold-active prophylaxis (EPO). At time of HSCT, high-risk conditions include the following: (1) IFD prior to HSCT, particularly those caused by molds, and (2) unrelated donor CBT or HSCT from an HLA-haploidentical family donor (EPO). After HSCT, high-risk conditions include the following: (1) severe acute or extensive chronic GvHD, (2) prolonged (&gt;3 weeks) or recurrent severe neutropenia due to any cause, (3) receipt of steroids &gt;2 mg/kg/day for at least 1 week, and (4) recurrent CMV infection requiring ganciclovir therapy (EPO).</td>
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<tr>
<td>Antifungal prophylaxis</td>
<td>Primary systemic antifungal prophylaxis is recommended for all patients, should start together with the conditioning regimen (Al), and should be maintained until day 75 (EPO). Fluconazole (400 mg/day intravenously or orally) is the drug of choice for patients at standard risk for IFD in the early phases after transplantation (Al). In patients at high-risk for IFD in the early phases after transplantation, intravenous mold-active antifungal drugs might be considered (EPO). Itraconazole may be effective, but tolerability and drug-drug interactions limit its use (B-II). Although intravenous itraconazole or an echinocandin may be used in this setting, LipAmB may be a more attractive option, considering its drug interaction profile, antimicrobial spectrum, and local experiences (EPO). Posaconazole (600 mg/day orally) is the drug of choice for patients with severe GvHD requiring treatment (Al).</td>
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<tr>
<td>Secondary antifungal prophylaxis</td>
<td>Patients with a history of IFD should receive secondary antifungal prophylaxis from the beginning of conditioning and during the period of severe neutropenia, during immunosuppressive therapy, and/or until immune reconstitution (Al).</td>
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<td>Monitoring of patients under antifungal prophylaxis</td>
<td>A surveillance strategy and/or an active diagnostic approach are recommended (EPO). Surveillance is a monitoring strategy for patients who are at high risk but have no signs or symptoms suggestive for a diagnosis of IFD. Active diagnostic approach is defined as a strategy for patients with signs or symptoms and/or microbiologic data possibly related to a fungal infection. In patients at high-risk for IFD, both surveillance and an active diagnostic approach are required. In patients with standard risk for IFD, only an active diagnostic approach is recommended (EPO).</td>
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<tr>
<td>Unexpected antifungal therapy</td>
<td>Empirical therapy may be administered to persistently febrile and neutropenic patients at high risk for IFD, without signs or symptoms specifically suggestive of an IFD, and who do not respond to 4–7 days of antibacterial therapy (BII). The lack of documentation of IFD in an empirical antifungal approach must follow a proper microbiological and clinical diagnostic effort. The empirical approach cannot be a remedy for an inadequate surveillance and diagnostic strategy (EPO). LipAmB or caspofungin are drugs of choice for empirical therapy (Al).</td>
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<tr>
<td>Preemptive antifungal therapy</td>
<td>Preemptive therapy is an early diagnostic-driven treatment, triggered by the results of a surveillance approach. The choice of the antifungal drug derives from the level of etiological documentation and should consider the spectrum of the drug and the various fungal pathogens possibly involved (EPO).</td>
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<td>Therapy for aspergillosis</td>
<td>Voriconazole is the drug of first choice for probable and proven invasive aspergillosis, including intracranial localization (Al), and LipAmB can be a suitable alternative (Al). For salvage therapy, agents include lipid formulations of amphotericin B (Al), posaconazole (B-II), itraconazole (B-III), caspofungin (BII), and micafungin (B-II). A combination therapy could be a reliable option for patients with worsening condition as a salvage therapy (BII). The most attractive combination in aspergillus infections includes the use of an echinocandin with either an azole or amphotericin B (EPO).</td>
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<tr>
<td>Treatment may be discontinued in patients who have complete resolution of infection and immune recovery (EPO).</td>
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<tr>
<td>Therapy for candidiasis</td>
<td>An echinocandin (caspofungin [Al], micafungin [AlII], or anidulafungin [AlIII]) or a lipid formulation of amphotericin B [Al] is recommended during neutropenia and in patients with critical conditions or with deep-seated candidiasis or when the species identification or susceptibility of the pathogen is unknown. Fluconazole (12 mg/kg/day) can be used for patients who are not critically ill and who have had no recent azole exposure (AlIII). Candidemia without obvious metastatic complications requires treatment for at least 2 weeks after the last positive blood culture result, but invasive candidiasis may require treatments throughout the duration of residual immunosuppression (AlIII). Catheter should be removed whenever possible in every case of candidemia, especially in nonneutropenic patients and when venous line infection is suspected (AlIII).</td>
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<td>Therapy for zygomycosis</td>
<td>Initial treatment should be performed using LipAmB B. High dosages (at least 5 mg/kg/day) may be required (EPO). Posaconazole is suitable for long-term suppressive treatment because of its relatively low toxicity and oral administration (EPO).</td>
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</tbody>
</table>

NOTE. This table provides a summary of recommendations already provided by the Infectious Diseases Society of America (IDSA) Guidelines [15–17] and those derived from the Gruppo Italiano Trapianto di Midollo Osseo Consensus. For recommendations already given by the IDSA Guidelines, the rate is reported according to the IDSA grading system for ranking recommendations not clearly supported by literature evidence but derived from the present consensus process were not rated and were identified as a result of the Expert Panel Opinion (EPO). CBT, cord blood transplant; CMV, cytomegalovirus; GvHD, graft-versus-host disease; HLA, human leukocyte antigen; LipAmB, liposomal amphotericin B.
absence of therapeutic drug monitoring facilities for antifungal drugs should not prevent physicians from using these drugs (EPO). The appropriate duration of monitoring for each drug has not been defined to date.

Research issues

The Expert Panel discussed which important issues deserved top priority for further investigation in allo-HSCT.

1. Adoptive cell therapy and vaccination therapies with dendritic cells aimed at restoring pathogen-specific immunity are attracting the attention of several investigators, and preliminary data obtained from patients who had previously received a T cell–depleted HSCT from an HLA-haploidentical relative and who were given donor-derived CD4+ cell clones that were specifically reactive against *Aspergillus* antigens has demonstrated the feasibility and partial effectiveness of this approach [60–62].

2. Identification of genetic and immunologic tests that are able to document the capacity of certain individuals to efficiently defend against IFD, such as the definition of mannose-binding lectin pathways and toll-like receptor polymorphisms [63–65], are warranted for the purpose of tailoring antifungal prophylaxis and duration of therapy.

3. Different approaches to combination therapy for IFD need to be tested in well-conducted, controlled clinical trials.

Conclusions

The existing scientific literature about the management of IFDs in allo-HSCT does not provide strong evidence-based recommendations in the various clinical settings associated with transplantation. Recent guidelines on prophylaxis and treatment of IFD in HSCT recipients offer indications that cannot be extended to different types of transplants and phases of transplantation, and most clinical decisions taken by physicians derive from personal experience and subjective considerations. In the present report, experts in the field judged whether the body of evidence was sufficient to provide any recommendation in a decision process, based on the idea that the risk/benefit ratio for any decision is the result of a partially subjective process. As a consequence, consensus was a critical part of producing the present recommendations. The recommendations already provided by the IDSA Guidelines [15–17] and those derived from the GITMO Consensus have been summarized in Table 3.

The definition of the level of risk for IFD, particularly those IFDs caused by molds, associated with the various types of transplant and phases of transplantation and the implementation of surveillance and diagnostic strategies are the critical determinants of the antifungal prophylactic and therapeutic strategies, respectively, in allo-HSCT recipients.

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