Primary Antifungal Prophylaxis in Adult Hematopoietic Stem Cell Transplant Recipients: Current Therapeutic Concepts

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In recipients of hematopoietic stem cell transplants (HSCTs), the mortality associated with invasive fungal infections (IFIs) remains high, despite the introduction of broad-spectrum antifungal agents over the past 2 decades. Preventing exposure to fungal pathogens in this population is impossible; therefore, clinicians have focused on prophylactic use of antifungal agents to prevent IFIs in high-risk HSCT recipients. It is important to target antifungal prophylaxis by type of HSCT (autologous or allogeneic), local epidemiology, and risk factors for IFIs so that patients can receive the most appropriate agent while balancing costs and the risks of toxicity, and minimizing the development of resistance. To assist clinicians in weighing the pros and cons of currently available antifungal agents when choosing a suitable prophylactic regimen, we provide a review of several key prospective randomized trials that evaluated various antifungal agents for primary prophylaxis in adult HSCT recipients. In addition, we describe the epidemiology of and risk factors for IFIs in HSCT recipients, the difficulties in diagnosing IFIs, antifungal agents used for prophylaxis, and the goals of primary prophylaxis. Fluconazole remains the gold standard for primary prophylaxis in autologous HSCT recipients. For allogeneic HSCT recipients, the agent chosen for prophylaxis must be based on the patient's risk factors for IFIs. In low-risk patients, fluconazole is an appropriate agent to use for primary prophylaxis immediately after transplantation. However, in allogeneic HSCT recipients who develop complications, such as graft failure, graft-versus-host disease, or cytomegalovirus infection, prophylaxis with a mould-active agent should be used.

Key Words: prophylaxis, antifungals, invasive fungal infection, IFI, hematopoietic stem cell transplant, HSCT, azoles, echinocandins, amphotericin B, immunosuppression.

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OUTLINE

Patients receiving hematopoietic stem cell transplants (HSCTs) are at increased risk for opportunistic infections with bacterial, viral, and

in particular, fungal pathogens. The mortality associated with invasive fungal infections (IFIs) in HSCT recipients remains high, despite the introduction of broad-spectrum antifungal agents over the past 2 decades. Since preventing exposure to fungal pathogens is impossible, clinicians have focused on the prophylactic use of antifungal agents to prevent IFIs in HSCT recipients at high risk for these infections, such as patients who experience prolonged neutropenia, recipients of transplants from unmatched related donors or matched unrelated donors, or patients with graft-versus-host disease (GVHD). Administration of prophylactic antifungal agents may expose patients to unnecessary drugs, pose a risk of toxicity, and lead to the emergence of resistant pathogens; however, current limitations in the diagnosis of fungal infections, and the high mortality associated with them, warrant the use of primary antifungal prophylaxis in high-risk HSCT recipients.[1]

An ideal prophylactic antifungal agent would have a broad spectrum of antifungal activity, including *Candida* species and moulds, with a high threshold for the development of resistance. It would be available both intravenously and orally, with 100% bioavailability with or without food. In addition, it would neither require dosage adjustments for patients with renal or hepatic impairment nor plasma concentration monitoring, and would have minimal adverse effects or drug interactions. Unfortunately, such an ideal agent does not yet exist, and clinicians must weigh the pros and cons of currently available antifungal agents to choose a suitable prophylactic regimen for HSCT recipients.

The epidemiology of IFIs in this patient population has changed over the past 2 decades. More HSCT recipients are developing IFIs due to non–*Candida albicans* yeasts or moulds, such as *Aspergillus* species or Zygomycetes. The availability of newer agents, such as voriconazole, posaconazole, and the echinocandins, that demonstrate activity against non–*C. albicans* yeasts, *Aspergillus* species, and (for posaconazole) the Zygomycetes, has renewed the debate among clinicians regarding the most appropriate antifungal agent for primary prophylaxis in this patient population.

For many years, fluconazole has been the antifungal drug of choice for primary prophylaxis in HSCT recipients. It provides excellent antifungal activity against *C. albicans,* the most common cause of IFIs, and has proved superior in the prevention of invasive *Candida* infections compared with topical agents (clotrimazole and nystatin) and oral (nonabsorbable) amphotericin B.[2, 3] The introduction of itraconazole provided a therapeutic option for patients at high risk for IFIs due to *Aspergillus* species; however, its poor oral bioavailability and drug interaction profile made it a less desirable agent for prophylaxis in HSCT recipients.

We performed a search of the PubMed database by using the following key words: hematopoietic stem cell transplant, peripheral blood stem cell transplant, bone marrow transplant, antifungal prophylaxis, fungal prophylaxis, and invasive fungal infections. Our search was limited to prospective, randomized clinical trials that included adult HSCT recipients, and review articles, case reports, and abstracts from 1966–August 2009 reported in the English language. Studies that included less than 12% HSCT recipients or included only topical agents (clotrimazole, nystatin), oral amphotericin B, or ketoconazole were excluded. In this review, we compare and contrast the key prospective, randomized, clinical trials examining antifungal agents for primary prophylaxis in adult HSCT recipients, with an emphasis on studies that have guided therapy to the present day. We also review the epidemiology of IFIs, obstacles in diagnosing IFIs, the risks and benefits of antifungal prophylaxis, and key factors to consider when choosing an antifungal agent for primary prophylaxis in this patient population.

Epidemiology of Invasive Fungal Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation

Risk Factors

Hematopoietic stem cell transplantation is a collective term used to describe bone marrow transplantation, peripheral blood stem cell

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transplantation, or umbilical cord blood cell transplantation. Recipients of HSCTs have numerous risk factors that predispose them to IFIs. The interplay among host risk factors, environmental exposure, and the net state of immunosuppression of the patient influences the overall risk for IFIs. Host risk factors include older age at the time of transplantation (because of the natural decline in immune system function with age), comorbidities such as diabetes mellitus, colonization with fungi, iron overload, splenectomy, and duration and severity of neutropenia.[4–7]

Environmental exposures that may occur during the pre- and posttransplantation period, such as exposure to airborne moulds or water sources and foods contaminated by or containing fungi, are potential sources of IFIs. In addition, most patients have compromised mucocutaneous barriers because of conditioning (or preparative) regimens—chemotherapy and/or radiation therapy administered to prepare the HSCT recipient to receive the donor's bone marrow—and central venous catheters that may facilitate the translocation of *Candida* species from the skin or gastrointestinal tract. Furthermore, HSCT recipients often receive broad-spectrum antibiotics that can alter the normal gastrointestinal flora, creating environmental conditions that are optimal for the growth of fungi.[4, 6]

The net state of immunosuppression of a patient is influenced by the type of preparative regimen received before transplantation, the agents used for the prevention and treatment of GVHD, or infection with immunomodulating viruses. Agents used for conditioning or to prevent or treat GVHD, such as fludarabine, antithymocyte globulin, alemtuzumab, rituximab, calcineurin inhibitors, infliximab, basilizimab, daclizumab, etanercept, sirolimus, or corticosteroids, may inhibit T- and/or B-lymphocyte function or affect tumor necrosis factor-α or interleukin-2. All of these agents contribute to impaired humoral- and/or cell-mediated immunity and are known to, or in theory, increase the risk for IFIs. Finally, coinfection with cytomegalovirus or Epstein Barr virus increases the risk for IFIs, as these viruses suppress T- and B-lymphocyte function. In particular, infection with cytomegalovirus or respiratory virus infections (respiratory syncytial virus and parainfluenza or influenza virus) increases the risk of late-onset invasive aspergillosis.[4-8]

The type of transplant a patient receives and the source of the cells also influence the risk for IFIs. In general, autologous transplant recipients have a lower risk for IFIs than do allogeneic transplant recipients. For both autologous and allogeneic HSCT recipients, the risk for IFIs increases in patients who experience prolonged neutropenia, receive ex vivo CD34 selection, or develop cytomegalovirus.[6] Allogeneic transplant recipients have additional risk factors that increase susceptibility to IFIs compared with autologous transplant recipients. To start, allogeneic transplant recipients have a slower reconstitution of cell-mediated immunity, especially when GVHD is present, after transplantation.[6, 8–10] Further, patients who receive T-cell–depleted transplants are unable to develop antigen-specific T-cell responses after transplantation, which hinders the immune response to fungi.[11] Moreover, recipients of human leukocyte antigen (HLA) unmatched related donor or matched unrelated donor cells are at higher risk for IFIs.[6, 8] Genetic polymorphisms in genes encoding interleukin-10, tumor necrosis factor receptor type 2, and toll-like receptors 1, 4, and 6 are also associated with a higher risk of invasive aspergillosis.[8] Finally, the source of hematopoietic cells influences the risk of IFIs in allogeneic transplants: HLA-matched related peripheral stem cell transplant recipients have a lower risk for IFIs than do patients receiving matched related bone marrow or cord blood cell transplants.[6]

Causative Pathogens

Classically, the pathogens responsible for IFIs in HSCT recipients have been primarily *Candida* and *Aspergillus* species. In a retrospective study of HLA-identical sibling allogeneic HSCT recipients, the frequency of IFIs from 1996–2000 was 14%, despite most patients having received antifungal prophylaxis with fluconazole, itraconazole, or amphotericin B. Invasive candidiasis occurred in 3% of patients, whereas non-*Candida* IFIs, primarily *Aspergillus* infections, occurred in 12% of patients.[10] In a recent large multicenter study, the cumulative incidence of proven or probable aspergillosis 12 months after autologous HSCT was 0.5%. The cumulative incidence of proven or probable aspergillosis at 12 months after HSCT was greater in allogeneic HSCT recipients: 2.3% for HLA-matched related donors, 3.2% for HLA-mismatched related donors, and 3.9% for transplants from unrelated donors. Earlier studies are difficult to compare with newer

studies due to differences in definitions for invasive aspergillosis.[7] More than half of the IFIs reported in this study were caused by *Aspergillus fumigatus*.[12]

When assessing an HSCT recipient for antifungal prophylaxis, it is important to consider the time frame since transplantation, as this will impact the likelihood of each fungal pathogen (Figure 1).[13] Engraftment, at which time the absolute neutrophil count (ANC) has increased to greater than 500–1000 cells/mm^3, usually occurs on or before approximately day 30 after transplantation, and may be influenced by the use of growth factors. During the preengraftment period, patients are neutropenic and may have breaks in their mucocutaneous barrier, placing them at high risk for infections due to *Candida* species. A smaller, yet significant number of invasive mould infections (IMIs), such as aspergillosis, are observed in this period, particularly in patients with delayed neutrophil engraftment and those administered T-cell–depleted or CD34-selected stem cell products.[6] *Candida* infections continue to occur in the postengraftment period; however, in the postengraftment and late-phase periods, impaired cell-mediated immunity, infection with immunomodulating viruses, GVHD, and immunosuppressive agents used to prevent or treat GVHD increase a patient's susceptibility to IMIs due to *Aspergillus* species as well as other moulds such as Zygomycetes.[6, 7]

Pathogenesis of *Candida* Infections

Candida infections in HSCT recipients usually occur within the first 100 days after transplan-

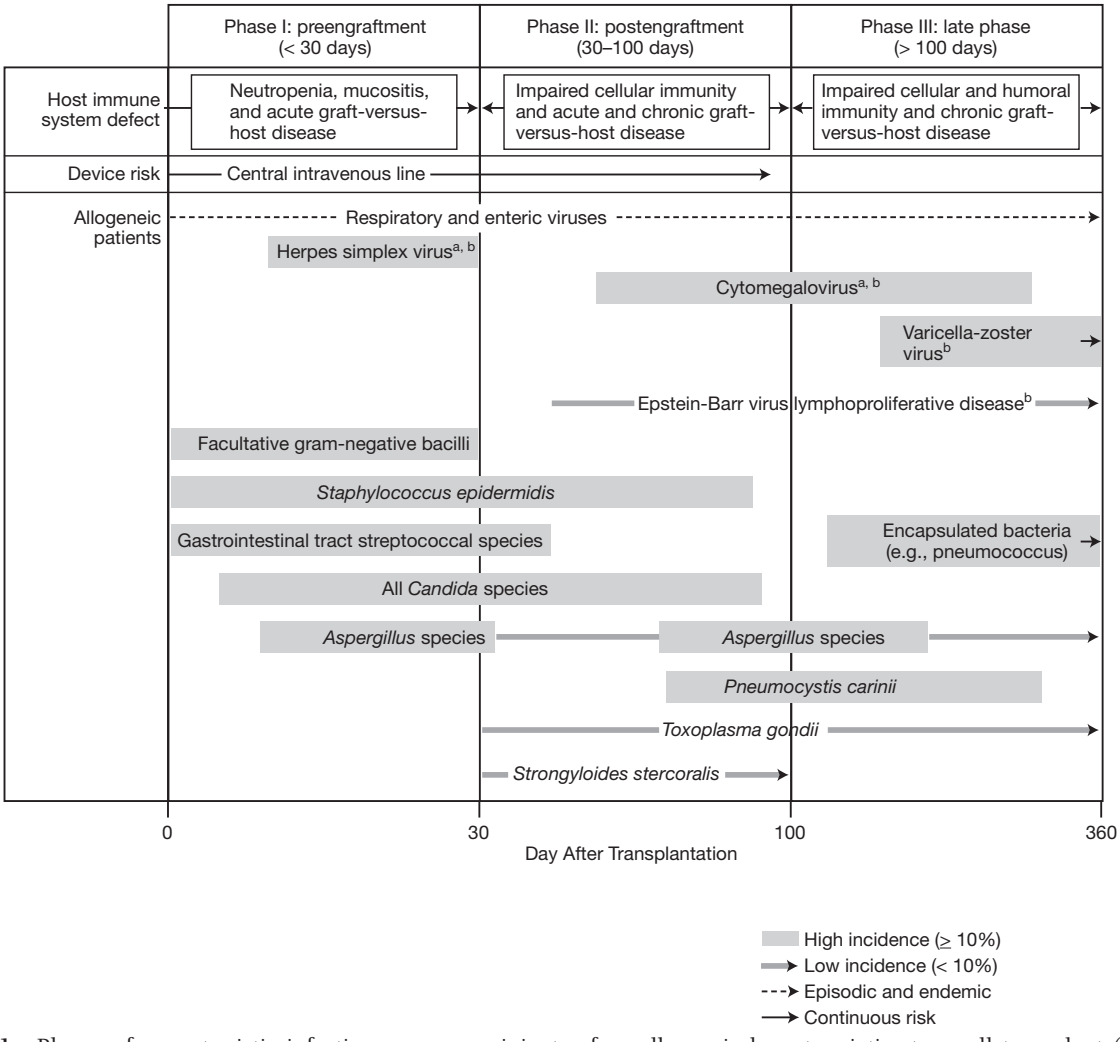

Figure 1. Phases of opportunistic infections among recipients of an allogeneic hematopoietic stem cell transplant (HSCT). [a]May occur without standard prophylaxis. [b]Occurs primarily among persons who are seropositive before transplantation.

tation, spanning the pre- and postengraftment period, mainly as a result of neutropenia and disrupted macrophage function.[13] Recently, investigators demonstrated that patients bearing the DECTIN-1 Y238X polymorphism had increased oral and gastrointestinal colonization with *Candida* species, rendering them at increased risk for fungal infections.[14] Translocation of *Candida* species across the gastrointestinal mucosa that has been damaged by chemotherapy or GVHD, or from the skin through central venous catheters, are the most common pathogenic routes of infection. The risk of *Candida* infections decreases after day 100, as patients have restored neutrophil and macrophage function and catheters have usually been removed by this time.[15]

Pathogenesis of *Aspergillus* and Other Mould Infections

Mould infections in HSCT recipients are primarily caused by environmental exposure. Preventive measures include high-efficiency particulate air filters, restriction on the use of showers, and avoidance of foods containing moulds during the high-risk period. Although environmental protection from fungal pathogens is a key component for preventing IFIs, it is impossible to maintain patients in sterile environments throughout the entire recovery period after transplantation, justifying the use of antifungal agents as prophylaxis. There is a bimodal pattern in the frequency of IMIs in HSCT recipients, with a lower rate in the preengraftment period, due to neutropenia, and then a higher rate in the postengraftment and late-phase periods, due to impaired cell-mediated immunity and GVHD and its associated therapy.[6, 8, 15]

Changing Epidemiology

The epidemiology of IFIs in HSCT recipients continues to evolve. Although there has been a decrease in IFIs caused by *C. albicans* as a result of fluconazole prophylaxis, patients may now be at an increased risk for IFIs due to non–*C. albicans Candida* species. The IFIs due to non–*C. albicans Candida* species, such as *Candida glabrata*, *Candida krusei, Candida tropicalis, Candida parapsilosis,* and *Candida lusitaniae,* and *Candida* isolates resistant to azoles have been reported.[16, 17] Furthermore, IFIs caused by species of *Aspergillus* other than *fumigatus* have also been described.[18, 19] The IFIs caused by such pathogens have been described only in case reports thus far, making it difficult to obtain a sense of whether there has been an increase in incidence and whether this is directly linked to the widespread use of newer antifungals such as voriconazole or echinocandins as prophylaxis.

In addition to shifts in the species of *Candida* and *Aspergillus* causing IFIs, an increased incidence of IFIs caused by Zygomycetes, including species of *Absidia*, *Mucor*, *Rhizomucor*, and *Rhizopus*, has been noted. Although these pathogens were noted to increase after the introduction of fluconazole for prophylaxis, some investigators have postulated that these more recent increases are attributable to the selective pressure of more broad-spectrum antifungals such as voriconazole and the echinocandins, which cover *Aspergillus* species but lack coverage of Zygomycetes, and/or the use of more potent immunosuppressive regimens.[20, 21] Several case reports and an observational case-control study of allogeneic HSCT recipients have documented the development of zygomycosis in patients who received voriconazole or caspofungin prophylaxis or therapy.[17–24] They noted that, in general, before use of these newer antifungal agents, zygomycoses had been noted only rarely in HSCT recipients. However, whether a true increase in zygomycoses exists is uncertain, and if present, whether the increase is attributable to the increased use of voriconazole or echinocandins is unclear. The use of more potent immunosuppressive agents, changes in the methods and types of transplantation, and other comorbidities may also contribute to increasing a patient's risk for these infections.

Mortality

Mortality due to IFIs in HSCT recipients is difficult to quantify, as the definition of an IFI varies among studies, and there are additional confounding factors, including the type of transplantation (autologous or allogeneic, peripheral stem cells or bone marrow cells). Despite administration of antifungal prophylaxis to most HSCT recipients, crude and attributable mortality due to *Candida* bloodstream infections is 32% and 42%, respectively; mortality increases to approximately 88% with organ or deep tissue (e.g., liver, kidney) involvement.[5, 25] For HSCT recipients with a diagnosis of invasive aspergillosis, the 3-month post-HSCT mortality rate is 53.8% for autologous transplant recipients but approaches 90% for allogeneic HSCT recipients.[12, 26] However, the overall 1-year survival rate is only about 20% for autologous and allogeneic HSCT recipients

with proven or probable invasive mould infections.[27]

Diagnosis of Invasive Fungal Infections

The diagnosis of IFIs in HSCT recipients is challenging; in addition, there are inconsistencies in the criteria defining an IFI. The Invasive Fungal Infections Cooperative Group from Europe and the Mycoses Study Group in the United States have developed (and recently updated) definitions for clinical researchers to use when investigating IFIs in patients with cancer and in HSCT recipients.[28] A proven IFI is defined as a positive fungal culture or histologic demonstration of fungal or hyphal elements in a biopsy from a sterile site with systemic signs and symptoms of infection. Probable and possible IFIs are further defined on the basis of specific host factors, clinical manifestations of fungal infection, and mycologic findings and are discussed further elsewhere.[29] Although these definitions are used to standardize enrollment of patients in clinical trials and are not meant to guide clinical practice, they further underscore the difficulties in diagnosing IFIs in immunocompromised patients.

Recipients of a HSCT may have blunted or nonspecific signs and symptoms of infection because of impaired inflammatory responses.[11] Generally, patients are febrile, and dyspnea and chest pain are common symptoms as the lungs are the most common organ affected in IMIs. However, disseminated infection is common, particularly in recipients of allogeneic HSCTs, and involvement of the central nervous system is observed in a significant number of patients.[7]

Distinguishing between colonization and infection is challenging. Cultures positive for species of *Candida* or *Aspergillus* from sterile sites are indicative of infection. However, the challenge occurs when these pathogens are cultured from nonsterile sites. For example, isolation of *Aspergillus* species from bronchial washings, sputum, or nasal secretions may not always indicate an invasive pulmonary or sinus *Aspergillus* infection.[11] Urinary candidiasis, although rarely the source of subsequent dissemination, may be a marker of acute hematogenous dissemination in neutropenic patients. A definitive diagnosis of invasive pulmonary aspergillosis can be made by obtaining a biopsy of lung tissue; however, thrombocytopenia often limits a clinician's ability to perform this procedure in HSCT recipients. Generally, the diagnosis is determined with the use of high-resolution computed tomography, in which invasive pulmonary aspergillosis will manifest early on as a nodular opacity with surrounding attenuation, or "halo sign." In late invasive aspergillosis, nodular lesions, diffuse pulmonary infiltrates, consolidation, or ground-glass opacities can be observed.[7, 11] These signs are not specific to invasive pulmonary aspergillosis, however, as bacteria and other fungal infections may produce similar findings.

New laboratory methods for detecting IFIs are being considered since other diagnostic methods may not always be definitive. A test that allows for early differentiation of IFIs due to *Aspergillus* species versus Zygomycetes and other moulds would be helpful to clinicians in the earlier initiation of appropriate antifungal therapy. Testing based on polymerase chain reaction is being performed in some centers and appears promising; however, no U.S. Food and Drug Administration (FDA)–approved method is commercially available.

The galactomannan test is an enzyme-linked immunosorbent assay that detects galactomannan, an antigen released from *Aspergillus* hyphae on invasion of host tissue. The utility of this assay has been assessed in the clinical setting by sampling serum, bronchoalveolar lavage fluid, cerebrospinal fluid, and pleural fluid; however, the currently approved test is performed on serum. The test has a sensitivity ranging from 30–100% and a specificity of approximately 85%; however, the sensitivity of the assay is decreased in patients receiving mould-active drugs on the day of sampling.[11] False-positive results can occur, particularly in patients receiving cyclophosphamide or piperacillin-tazobactam,[30, 31] and differences exist in the cutoff values for a positive result between the United States and Europe. False-negative results can occur during the concomitant use of antifungals, presumably because the level of galactomannan is related to the fungal burden.[11] In addition, it is important to note that the utility of galactomannan testing in the setting of prophylaxis has not been defined.

1,3-β,D-Glucan is a component of fungal cell walls that can be detected colorimetrically in clinical samples, including blood and bronchoalveolar lavage specimens. However, the current FDA-approved test is performed only on serum. The 1,3-β,D-glucan test can be used to detect most fungi, except for Zygomycetes and cryptococci, with a sensitivity of 55–100% and a

Table 1. Comparison of Antifungal Agents[32, 33]

Characteristic	Amphotericin B	Fluconazole	Itraconazole OS	Voriconazole	Posaconazole
Antifungal activity					
Candida sp	Yes[a]	Yes[b]	Yes	Yes	Yes
Aspergillus sp	Yes[c]	No	Yes	Yes	Yes
Zygomycetes	Yes	No	No	No	Yes
Cryptococcus neoformans	Yes	Yes	Yes	Yes	Yes
Formulation	i.v.	i.v., p.o.	p.o.[d]	i.v., p.o.	p.o.
Oral bioavailability	NA	> 90%	~55%	~96%	NA
Give oral formulation with or without food	NA	With or without food	Without food	Without food	With fatty food
Dosage adjustment					
Renal impairment	Yes	Yes	No[e]	Not for p.o.[e]	No
Hepatic impairment	No	No	No	Yes	No
Drug interactions	Minor	Moderate	Major	Major	Major
CYP enzymes	No	3A4, 1A2, 2C8/9	3A4	3A4, 2C9, 2C19	3A4
Plasma concentration monitoring suggested	No	No	Yes	Yes	Unclear
Cost/day (AWP)	< $50 to > $100	< $50	< $50	$50–100	$50–100
Adverse effects					
Renal	Yes	No	No[e]	With i.v. only[e]	No
AST or ALT level elevation	No	Yes	Yes	Yes	Yes
Abdominal[f]	No	Yes	Yes	Yes	Yes
Infusion-related	Yes	No	No	No	No
Visual	No	No	No	Yes	No
Rash	No	Yes	Yes	Yes	Yes

OS = oral solution; NA = not applicable; CYP = cytochrome P450; AWP = average wholesale price; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

[a]Amphotericin B has no in vitro activity against *Candida lusitaniae*.

[b]Fluconazole has no in vitro activity against *Candida krusei* and has dose-dependent activity against *Candida glabrata*.

[c]Except *Aspergillus terreus*.

[d]Intravenous itraconazole was discontinued in the United States in 2008.

[e]Intravenous itraconazole is not recommended in patients with creatinine clearance < 30 ml/min; i.v. voriconazole is not recommended in patients with creatinine clearance < 50 ml/min.

[f]Abdominal adverse effects include anorexia, nausea, vomiting, diarrhea, or abdominal pain.

specificity of 52–100%. However, the test can produce false-positive results in patients undergoing hemodialysis with cellulose membranes, as well as in other cases for unclear reasons.[11] One way to effectively use the 1,3-β,D-glucan or galactomannan assays may be to serially screen patients who are at high risk for IFIs and/or use them to monitor response to therapy as, for instance, galactomannan results decline in patients responding to treatment.[7, 11]

Goals of Antifungal Prophylaxis

Before delving into a discussion about prophylaxis, it is important to distinguish between the different approaches to the management of IFIs in HSCT recipients. Primary prophylaxis provides patients (who have never had an IFI in the past) at high risk for IFIs with an antifungal regimen selected specifically to prevent IFIs. Secondary prophylaxis, which is not discussed as it is beyond the scope of this article, refers to providing a patient who has a history of an IFI with an antifungal agent to prevent a recurrence of the IFI during subsequent episodes of neutropenia or immunosuppression. By contrast, preemptive therapy is triggered on detection of an early indicator suggestive of an IFI, such as fungal antigens or metabolites, colonization of the respiratory tract with *Aspergillus* species, or the appearance of a halo sign on a high-resolution computed tomography scan. Empiric therapy refers to the addition of an antifungal agent if a patient has had a fever that is unresponsive to broad-spectrum antibiotics for 72–96 hours. Finally, treatment is the term applied when an antifungal agent is used for a documented IFI.

The goal of primary antifungal prophylaxis in HSCT recipients is to prevent morbidity and mortality from IFIs, as early diagnosis is difficult and treatment of IFIs is challenging. Recovery of neutropenia, remission of the hematologic malignancy, and prolonged antifungal therapy are necessary for cure. A secondary goal is to reduce

Table 1. (continued)

Caspofungin	Micafungin	Anidulafungin
Yes	Yes	Yes
Yes	Yes	Yes
No	No	No
No	No	No
i.v.	i.v.	i.v.
NA	NA	NA
NA	NA	NA
No	No	No
Yes	No	No
Minor	Minor	Minor
No	No	No
No	No	No
$50–100	$50–100	$50–100
No	No	No
Yes	Yes	Yes
No	No	No
Yes	Yes	Yes
No	No	No
Yes	Yes	Yes

fungal colonization. However, the risks of prophylaxis must also be weighed in deciding whether patients should receive prophylaxis, and if so, the specific antifungal agent and duration of antifungal therapy. Toxicity due to the antifungal agent, promotion of resistance, selection of fungi not covered by the antifungal resulting in a shift from one fungal species to another, increasing the potential for drug interactions, and cost are all factors that need to be considered before initiation of antifungal prophylaxis. Despite the risks involved with providing HSCT recipients with prophylaxis, the benefit of preventing morbidity and mortality due to IFIs warrants the use of primary antifungal prophylaxis in the highest risk patients. By targeting prophylaxis specifically to high-risk patients, taking into account the basal frequency of IFIs in the surrounding environment, host risk factors, type of HSCT received, specific therapeutic interventions received, and transplant complications, antifungal prophylaxis can be used appropriately without posing unnecessary risks.

Antifungal Agents

In addition to the results of clinical trials, when considering an antifungal agent for a specific patient, it is important to consider its spectrum of activity against fungal pathogens, mechanism of action, dosage adjustments for renal or hepatic impairment, adverse-effect profile, drug interaction potential, dosage formulation, oral bioavailability with or without food, the need for plasma concentration monitoring, and cost (Table 1).[32, 33] A more detailed description of the pharmacology of antifungal agents is published elsewhere.[32]

Amphotericin B formulations, the triazoles, and the echinocandins all have activity against most *Candida* species. However, a few exceptions should be noted. Fluconazole has no activity against *C. krusei* or *Aspergillus* species and generally displays dose-dependent activity against *C. glabrata*. Despite initial in vitro sensitivity of *C. lusitaniae* to amphotericin B, its clinical use is often associated with failure because of the rapid development of acquired or inducible resistance. Whereas amphotericin B, itraconazole, voriconazole, posaconazole, and the echinocandins are active against *Aspergillus* species, only amphotericin B and posaconazole display activity against Zygomycetes.

Amphotericin B and the echinocandins are available only in intravenous formulations, whereas posaconazole and itraconazole are available only in oral formulations. The availability of both oral and intravenous formulations of fluconazole and voriconazole has made these agents easier to use in HSCT recipients, as the patient can be switched between dosage forms as needed. From a therapeutic standpoint, oral formulations of antifungal agents can reduce gastrointestinal flora, decreasing the possibility of translocation of *Candida* species (but not moulds) into the bloodstream. However, a counterargument is that altering the normal gastrointestinal flora may create conditions that are conducive to the growth of other fungi (e.g., non–*C. albicans* yeasts) or bacteria. The use of intravenous dosage forms increases cost and the risk of catheter-related line infections, but they may not have as great an impact on the gastrointestinal flora. Although the bioavailability of the oral formulations of fluconazole and voriconazole approach 100%, itraconazole oral solution is only about 55% bioavailable. Finally, the bioavailability and tolerability of these agents as well as the need for administration with meals should be taken into account. Posaconazole must be taken with a fatty meal to ensure absorption of the drug. Many patients have difficulty tolerating oral itraconazole solution because it needs to be administered on an empty stomach, and it causes

a lot of abdominal discomfort. Other patients may not be able to tolerate the visual disturbances caused by voriconazole.[32]

As HSCT recipients generally receive a large number of drugs after transplantation, it is necessary to evaluate the drug interaction potential of antifungal agents that are used for prophylaxis. The azole antifungal agents alter plasma concentrations of a number of other drugs (in particular, many immunosuppressive agents) that undergo metabolism by cytochrome P450 (CYP) enzymes. A more detailed description of these interactions is available elsewhere.[33] By contrast, amphotericin B and the echinocandins have few drug interactions.[32]

Plasma concentration monitoring may be necessary when using an antifungal for prophylaxis, to ensure efficacy, absorption, and safety. It is not necessary to monitor concentrations of amphotericin B or the echinocandins; however, monitoring serum concentrations (after 7 days of administration or after dosage changes) is recommended for itraconazole, voriconazole, and possibly posaconazole.[32, 34, 35]

As the bioavailability of itraconazole oral solution is suboptimal, plasma concentration monitoring (combining the concentration of itraconazole plus the active metabolite hydroxyitraconazole) is recommended to ensure that adequate absorption is achieved. The target range for itraconazole trough concentrations is at least 0.5–1 μg/ml.[32, 34, 36, 37]

Monitoring of plasma voriconazole concentrations is recommended because of its variable metabolism, to ensure adequate concentrations for prophylactic efficacy and prevent adverse events with supratherapeutic concentrations. Voriconazole concentrations of 2–6 μg/ml have been recommended; two studies have correlated plasma concentrations greater than 2.05 μg/ml with greater efficacy, and concentrations less than 0.25 μg/ml with failure to respond in the treatment of invasive aspergillosis.[35, 38] Higher plasma concentrations have been correlated with toxicity: trough concentrations greater than 5.5 μg/ml have been correlated with neurologic toxicity. However, whether these concentrations are applicable in the prophylaxis of fungal infections is not known.[32, 35, 38–43]

Although it is unclear whether posaconazole requires plasma concentration monitoring, it is likely that monitoring will be recommended, as its absorption is dependent on administration with a fatty meal and is highly variable in HSCT recipients, especially those with acute GVHD.[44] In a study that used oral posaconazole 200 mg 3 times/day for prophylaxis in patients with severe GVHD, among patients for whom the results of pharmacokinetic testing were available, the mean concentration of posaconazole was 1.470 mg/L in the 82 patients with chronic GVHD and 0.958 mg/L in the 158 patients with acute GVHD.[44] In the five patients who developed IFIs, median and peak plasma concentrations were 611 and 635 ng/ml, respectively, versus 922 and 1360 ng/ml, respectively, in the 241 patients without an IFI. The small number of subjects in the group who developed fungal infection precludes conclusions regarding a therapeutic range for prophylaxis of fungal infections, or the dosages of posaconazole required to achieve this range.

Comparative Studies

Before oral systemic antifungal agents such as fluconazole became available, clinicians used oral nonabsorbable antifungals (e.g., amphotericin B, nystatin, and clotrimazole) to prevent superficial fungal infections like oral thrush or esophagitis. These agents, however, were of little utility in preventing systemic IFIs and therefore are not discussed further except when they were used as comparators in studies that assessed oral absorbable azoles or intravenous antifungals.

Numerous studies have compared antifungal agents with placebo, nonabsorbable antifungals, or other systemic antifungals, for prophylaxis in both autologous and allogeneic HSCT recipients. In most studies, antifungal prophylaxis was begun at the start of or within 72 hours of the start of the conditioning regimen; however, the dosages and formulations of the antifungal agents and the durations of antifungal prophylaxis have been inconsistent. In particular, various dosages and formulations of fluconazole, itraconazole, and amphotericin B have been evaluated. Prophylaxis has been administered until engraftment (ANC > 500–1000 cells/mm^3 for 2–7 consecutive days) or until a predefined time point (~ 42–180 days) after HSCT, the development of intolerable adverse effects, or the occurrence of proven or probable IFIs or death. Study end points generally include the occurrence of proven IFIs, or the combined occurrence of proven, probable, or possible IFIs, although some studies include IFI-related mortality, adverse effects, compliance, breakthrough probable or proven IFIs, or initiation of antifungal therapy for empiric or probable or proven IFI. However, the definitions of proven, probable, and possible infection differ among

studies. Moreover, most studies were not sufficiently powered to enable determination of statistically significant differences between groups for each of these end points. Despite these limitations, the results of these studies have shaped clinical practice. Table 2 provides the descriptions and results, respectively, of the 26 trials we identified that evaluated various agents for primary antifungal prophylaxis in HSCT recipients, as discussed in the following sections.[2, 3, 36, 37, 45–66]

Fluconazole

Fluconazole was the first oral systemic antifungal agent to receive FDA approval for the prophylaxis of candidiasis in patients undergoing HSCT. Fluconazole offers the advantage of availability in both parenteral and oral formulations with systemic activity against a wide range of *Candida* species. Fluconazole was compared with placebo or oral nonabsorbable antifungals in seven randomized, comparative trials.[2, 3, 47–49, 52, 61] Despite differences in the number of autologous and allogeneic HSCT recipients, the duration of prophylaxis, and the dosages of fluconazole used in each study, significant decreases (8–14%) in proven IFIs were demonstrated in five studies (one of which included proven, probable, and possible IFIs) in patients who received fluconazole prophylaxis. [2, 3, 47–49]

Fewer IFI-related deaths were observed in the three studies[47–49] (among the five in which this end point was assessed[2, 47–49, 61]) in which patients received fluconazole 400 mg/day from the start of conditioning until day 60–75 after transplantation; however, only one of the five studies demonstrated a significant decrease in mortality. There was no benefit of fluconazole prophylaxis on overall mortality in four of the five trials that assessed this end point,[2, 48, 49, 52] with the one exception being the study[47] in which the fluconazole group had a 14.7% reduction in overall mortality (p value not reported) and a lower probability of death by day 110 (p=0.004). A potential reason for the overall mortality benefit observed in this study is that the patients were predominantly higher risk allogeneic HSCT recipients, compared with the other studies in which a balanced number of autologous and allogeneic HSCT recipients and/or patients with hematologic malignancies were evaluated. In a follow-up study 8 years later, a persistent survival benefit due to fluconazole (44.7% and 27.7 % in fluconazole- and placebo-treated patients, respectively, p=0.0001) was observed, and placebo treatment was independently associated with a relative risk of death of 1.5 (95% confidence interval 1.1–2).[67] However, a major limitation of the follow-up study was that the investigators were unaware of whether the patients had received fluconazole or other antifungal agents after having participated in the earlier trial.

Breakthrough IFIs with *C. krusei, Aspergillus* species, and Zygomycetes have occurred in patients receiving fluconazole prophylaxis. Independent risk factors for failure of fluconazole prophylaxis are older age, use of antibacterial prophylaxis, use of cytarabine plus anthracycline–based chemotherapy, and a high *Candida* colonization index.[49] Only one trial (discussed above)[47] commented on antifungal susceptibility testing. Of six breakthrough *C. glabrata* isolates that were resistant to fluconazole, two were isolated from patients who had received fluconazole prophylaxis, one of whom had been colonized with fluconazole-susceptible *C. glabrata* before beginning prophylaxis. A third isolate was from a patient who received placebo and had been colonized with fluconazole-resistant *C. glabrata* before the study. Finally, a *Candida guilliermondii* isolate from a patient who had received fluconazole prophylaxis was resistant to fluconazole.

In summary, fluconazole, at the dosages evaluated, decreases the frequency of IFIs due to *Candida* species, in particular *C. albicans*. However, there is concern that lower doses of fluconazole may not achieve adequate concentrations to exceed the minimum inhibitory concentrations for the treatment of *Candida* species such as *C. glabrata,* which typically demonstrate higher minimum inhibitory concentrations to azole antifungals than do *C. albicans*.[52] Fluconazole, at a dose of 400 mg/day, decreases mortality due to IFIs in HSCT recipients and has the additional benefit of improving overall survival in allogeneic HSCT recipients when a longer duration (to day 75 after transplantation) of prophylaxis is used,[47] and an enduring benefit persists even after discontinuation of fluconazole.[67]

Itraconazole

As fluconazole has no activity against *Aspergillus* species or other moulds, itraconazole was investigated as a prophylactic agent in the hopes

Table 2. Description of Comparative Trials of Antifungal Agents

Patient Population	Duration of Prophylaxis	Study Groups
356 patients Allogeneic BMT (n=171) Autologous BMT (n=185)[48]	During conditioning and until day 70 after transplantation Mean: fluconazole 22.6 days, placebo 19.7 days	Fluconazole 400 mg p.o. q.d. or 200 mg i.v. q12h Placebo p.o. or i.v.
536 patients (511 evaluable) HM (n=426) BMT (n=110)[3]	Before conditioning, until ANC > 1000/mm^3 or day 84 after transplantation	Fluconazole 50 mg p.o. q.d. Nystatin 4 x 10^6 U p.o. or amphotericin B 2 g p.o. q.d.
90 patients HM (n=67) BMT (n=23)[2]	Within 7 days of ANC < 1000/mm^3, until ANC > 1000/mm^3 x 3 days	Fluconazole 200 mg p.o. q.d. Clotrimazole 10-mg troche q12h
300 patients Allogeneic BMT (n=265) Autologous BMT (n=35)[47]	During conditioning, until day 75 after transplantation	Fluconazole 400 mg i.v. or p.o. q.d. Placebo i.v. or p.o.
89 patients HM (n=56) Allogeneic BMT (n=30) Autologous BMT (n=3)[61]	Not reported	Fluconazole 400 mg i.v. or p.o. q.d. Nystatin 24 x 10^6 U t.i.d. p.o. + inhaled miconazole t.i.d.
304 patients HM (n=184) Autologous BMT (n=120)[49]	During conditioning, until day 60 after transplantation	Fluconazole 400 mg p.o. q.d. Placebo p.o.
253 patients (early prophylaxis) Allogeneic BMT (n=142) Autologous BMT (n=111)[52]	During conditioning, until ANC ≥ 1000/mm^3 x 3 days	Fluconazole 400 mg p.o. q.d. Fluconazole 200 mg p.o. q.d.
172 patients (maintenance prophylaxis) Allogeneic BMT (n=95) Autologous BMT (n=77)[52]	Until ANC ≥ 1000/mm^3 x 3 days or day 100 after transplantation	Fluconazole 100 mg p.o. q.d. Clotrimazole 10-mg troche q.i.d.
405 patients HM (n=331) Autologous BMT (n=74)[50]	Before conditioning, until ANC > 1000/mm^3 or 56 days after transplantation	Itraconazole 2.5 mg/kg p.o. (solution) b.i.d. Placebo p.o.
445 patients HM (n=215) Allogeneic BMT (n=51) Autologous BMT (n=179)	During conditioning, until ANC ≥ 1000/mm^3 x 7 days	Itraconazole 2.5 mg/kg p.o. (solution) b.i.d. Fluconazole 100 mg p.o. (suspension) q.d.
202 patients HM (n=87) Autologous HSCT (n=115)[h, 62]	During conditioning, until ANC > 500/mm^3	Itraconazole 100 mg p.o. (capsule) b.i.d. Fluconazole 50 mg p.o. b.i.d.
210 patients HM (n=179) Autologous BMT (n=31)[63]	During conditioning until ANC > 1000/mm^3 x 3 days	Itraconazole 100 mg p.o. (capsule) q12h Placebo p.o.
140 patients (138 evaluable) Allogeneic HSCT (n=138)[h, 36]	Days 1–100 after transplantation	Itraconazole 200 mg i.v. q12h x 2 days, then 200 mg i.v. q.d. x 12 days, then 200 mg p.o. (solution) q12h Fluconazole 400 mg i.v. q.d. x 14 days, then 400 mg p.o. q.d.
304 patients (299 evaluable) Allogeneic HSCT (n=299)[h, 37]	During conditioning, until a minimum of 120 days (if GVHD, until 28 days after steroid use or day 180 after transplantation)	Itraconazole 2.5 mg/kg p.o. (solution) t.i.d. or 200 mg i.v. q.d. Fluconazole 400 mg p.o. or i.v. q.d.
195 patients HM (n=43) Allogeneic HSCT (n=44)[h] Autologous HSCT (n=108)[h, 45]	During conditioning, until resolution of neutropenia or to a maximum of 56 days after transplantation (mean 17 days, both groups)	Itraconazole 200 mg p.o. (solution) b.i.d. or 200 mg i.v. q.d. Fluconazole 400 mg p.o. or i.v. q.d.

Table 2. (continued)

IFI Rate, % (no.)	Pathogens Causing IFIs (no.)	Mortality Rate, % (no.)	
		Due to IFI	Overall
2.8 (5)	*C. albicans* + *C. tropicalis* (1), *Candida* sp (1), *Aspergillus* sp (1), *Aspergillus* sp + *C. parapsilosis* (1), Zygomycetes (1)	0.6 (1)	30.7 (55)[a]
15.8 (28) p<0.001	*C. krusei* (3), *Aspergillus* sp (1), Zygomycetes (1), *C. albicans* (11), *C. tropicalis* (5), *C. glabrata* (2), *C. lusitaniae* (2), *C. parapsilosis* (1)	5.6 (10) p<0.001	26.0 (46)[a] p=0.38
3.9 (10)	*C. krusei* (3), *A. fumigatus* (2), *Acremonium* sp (1)	NA	NA
12.2 (31) p=0.001	*C. krusei* (3), *C. albicans* (2), *C. tropicalis* (2), *C. rugosa* (1), Zygomycetes (1)	NA	NA
7.0 (3)[b]	*Aspergillus* sp (1), *Fusarium* sp (1), clinically documented IFI (1)	4.9 (2)[b]	14.2 (6)
22.0 (11)[b] p<0.05	*C. albicans* + *C. tropicalis* (1), *A. flavus* (1), *Aspergillus* sp (3), *Aspergillus* sp + *Alternaria* sp (1), *Aspergillus* sp + *C. krusei* (1), *Aspergillus* sp + *Fusarium* sp (1), *Acremonium* sp (1), clinically documented IFI (2), clinically documented IFI + *C. lusitaniae* (1)	18.8 (9)[b] p<0.06	16.7 (8) p=NS
7.0 (10)	*C. glabrata* (3), *C. guilliermondii* (1), *A. fumigatus* (3), *Fusarium* sp (1), unknown (2)	7.2 (11)	20.4 (31)[c]
18.0 (26) p<0.004	*C. albicans* (18), *C. glabrata* (6), *C. tropicalis* (2), *C. parapsilosis* (1), *C. pseudotropicalis* (1), yeast not specified (1), *A. fumigatus* (2), *Fusarium* sp (1)	12.8 (19) NA	35.1 (52)[c] NA
2.3 (1)	*A. fumigatus* (1)	2.3 (1)	NA
4.3 (2) p=NS	*Candida* sp (1), *Aspergillus* sp (1)	0 NA	NA
3.0 (4)	*C. albicans* (1), *C. krusei* (1), *Aspergillus* sp + *C. tropicalis* (1)	0.7 (1)	9.8 (15)
17.0 (22) p=0.0003	*C. albicans* (6), *C. krusei* (1), *C. tropicalis* (1), *C. lusitaniae* (1)	4.0 (6) p=0.04	9.9 (15) NA
8.0 (9)	*C. albicans* (1), *C. tropicalis* (2), *C. glabrata* (2), *A. fumigatus* (4), *A. glaucus* (1), *Aspergillus* sp (1)[d]	NA	19.0 (24)
2.0 (3) p=0.06	*C. glabrata* (1), *A. flaxus* (1), *Aspergillus* sp (1)[d]	NA	16.0 (20) NA
3.4 (3)	*C. krusei* (1), *A. fumigatus* (2), *A. fumigatus* + *A. nidulans* (1)[e]	NA	18.2 (16)
1.2 (1) NA		NA	16.7 (14) p=NS
2.5 (5)	*C. parapsilosis* (1), *A. fumigatus* (1), *A. flavus* (1), *Aspergillus* sp (1), *A. flavus* + *Fusarium* sp (1)	0.5 (1)	7.0 (15)
4.4 (9) p>0.2	*C. albicans* (3), *C. tropicalis* (3), *C. parapsilosis* (1), *Trichosporon capitatum* (1), *Aspergillus* sp (1)	2.5 (5) p=0.11	9.0 (18) NA
0.3 (1)[f]	*C. albicans* (1)	0 (0)[f]	1.0 (3)[f]
2.0 (6)[f] p=NS	*C. tropicalis* (1), *C. krusei* (1), *Aspergillus* sp (4)	1.4 (4)[f] NA	3.8 (11)[f] NA
7.9 (8)[g]	*A. fumigatus* (4), clinically documented IFI (4)	5.9 (6)[g]	10.9 (11)
11.0 (11)[g] NA	*A. fumigatus* (2), Zygomycetes (2), clinically documented IFI (7)	3.0 (3)[g] NA	6.9 (7) p=NS
4.8 (5)	*C. tropicalis* (1), *C. lusitaniae* (1), *Rhodotorula rubra* (1), *Exophiala jeanselmei* (1)	1.9 (2)	7.7 (8)
8.5 (9) p=0.28	*Candida* sp (3), *C. albicans* (1), *C. tropicalis* (1), *C. glabrata* (1), *A. fumigatus* (1), *E. jeanselmei* (1)	0.9 (1) NA	6.6 (7) p=0.76
9.0 (6)[d]	*C. glabrata* + *C. krusei* (1), *C. guilliermondii* (1), *Aspergillus* sp (3), Zygomycetes (1)	9.0 (6)	45.0 (32)[a]
25.0 (17)[d] p=0.01	*C. glabrata* (4), *C. krusei* (3), *C. tropicalis* (1), *Aspergillus* sp (8), *Fusarium* sp (1)	18.0 (12) p=0.13	42.0 (28)[a] p>0.2
13.0 (20)[b]	*C. glabrata* (2), *C. parapsilosis* (1), *A. fumigatus* (5), *Aspergillus* sp (2), *A. niger* + *Cunninghamella* sp (1)	8.0 (12)	23.8 (36)
16.0 (25)[b] p=0.46	*C. parapsilosis* (2), *C. glabrata* (1), *C. krusei* (1), *A. fumigatus* (11), *Aspergillus* sp (2), *A. terreus* (2), *A. niger* (1), *A. fumigatus* + *A. niger* (1)	7.0 (11) NR	19.2 (29) NR
11.0 (11)[g]	*C. glabrata* (1), *C. tropicalis* (1), *Aspergillus* sp (9)[l]	5.2 (5)[g]	29.2 (28)
12.0 (12)[g] p=NS	*C. krusei* (1), *Aspergillus* sp (11)[l]	9.1 (9)[g] p=NS	30.2 (30) p=NS

Table 2. Description of Comparative Trials of Antifungal Agents (continued)

Patient Population	Duration of Prophylaxis	Study Groups
182 patients Autologous BMT (n=182)[60]	Not reported	Amphotericin B 1 mg/kg i.v. q.d. Placebo i.v.
76 patients Allogeneic BMT (n=63) Autologous BMT (n=13)[59]	Initiated when ANC < 500/mm^3 x 2 days, until ANC > 500/mm^3 x 2 days or day 90 after transplantation	L-amphotericin B 1 mg/kg i.v. q.d. Placebo i.v.
35 patients Allogeneic BMT (n=24) Autologous BMT (n=11)[64]	Initiated when ANC ≤ 500/mm^3, until ANC > 500/mm^3 x 2 days	Amphotericin B 1 mg/kg i.v. q.d. Placebo i.v.
161 patients HM (n=26) Allogeneic BMT (n=85) Autologous BMT (n=50)[53]	During conditioning, until ANC > 500/mm^3 x 3 days	L-Amphotericin B 2 mg/kg i.v. 3x/wk Placebo i.v.
382 patients HM (n=318) Autologous BMT (n=64)[58]	Initiated at randomization, until ANC > 1000/mm^3 x 2 days or day 50 after transplantation	Aerosolized amphotericin B 10 mg b.i.d. No aerosolized prophylaxis
355 patients Allogeneic HSCT (n=103)[h] Autologous HSCT (n=252)[h, 51]	Initiated on day 1, until ANC > 500/mm^3	Amphotericin B 0.2 mg/kg i.v. q.d. (maximum 20 mg/day) Fluconazole 400 mg i.v. or p.o. q.d.
186 patients Allogeneic HSCT (n=140)[h] Autologous HSCT (n=46)[h, 56]	Initiated on day before conditioning, until ANC > 500/mm^3 x 3 days	Amphotericin B 0.2 mg/kg i.v. q.d. (maximum 10 mg/day) Fluconazole 200 mg p.o. q.d.
217 patients HM (n=189) Autologous HSCT (n=28)[h, 54]	Initiated 1–2 days before ANC < 500/mm^3, until ANC ≥ 500/mm^3	L-amphotericin B 50 mg i.v. q.o.d. No prophylaxis
271 patients HM (n=185) Allogeneic HSCT (n=30)[h] Autologous HSCT (n=56)[h, 66]	Initiated at randomization, until ANC > 300/mm^3 or maximum of 12 inhalations per neutropenic episode	Aerosolized L-amphotericin B 12.5 mg q.d. x 2 consecutive days/wk Placebo inhalation q.d. x 2 consecutive days/wk Patients also received fluconazole prophylaxis
882 patients (880 evaluable) Allogeneic HSCT (n=476)[h] Autologous HSCT (n=404)[h, 46]	Before conditioning, until ANC ≥ 500/mm^3 or day 42 after transplantation	Micafungin 50 mg i.v. q.d. Fluconazole 400 mg i.v. q.d.
600 patients Allogeneic HSCT (n=600)[h, 55]	Fixed 112-day treatment period	Posaconazole 200 mg p.o. (suspension) t.i.d. Fluconazole 400 mg p.o. q.d.
600 patients Allogeneic HSCT (n=600)[h, 65]	Days 0–100 or until day 180[p] after transplantation	Voriconazole 200 mg q12h p.o. or i.v. Fluconazole 400 mg p.o. or i.v. q.d.

of preventing IFIs from these pathogens as well as *Candida* species. However, the results of studies evaluating itraconazole for prophylaxis were difficult to evaluate, as several doses and formulations of itraconazole have been compared with a variety of agents. Similarly, a variety of end points have been assessed: proven IFIs; proven, probable, possible IFIs; proven IMIs and candidemia; and microbiologically and clinically documented IFIs.

Itraconazole prophylaxis in HSCT recipients has been evaluated in seven randomized studies.[36, 37, 45, 50, 57, 62, 63] Overall, the studies demonstrated no significant difference in IFI rates between itraconazole and fluconazole or placebo, with one exception.[36] This open-label trial of allogeneic HSCT recipients who received fluconazole or intravenous itraconazole followed by oral itraconazole solution, demonstrated a significant difference in the rate of proven IFIs (itraconazole 13% vs fluconazole 28%, p=0.03).[36] Unfortunately, the small sample size prevented an

Table 2. (continued)

IFI Rate, % (no.)	Pathogens Causing IFIs (no.)	Mortality Rate, % (no.)	
		Due to IFI	Overall
6.6 (6)[i]	Presumed IFI (2)	NA	3.3 (3)
17.6 (16)[i]	*Candida* sp (3), presumed IFI (2)	NA	12.1 (11)
NA			p<0.03
3 (1)	*C. guillermondi* (1)	2.8 (1)	44.4 (16)
8 (3)	*C. albicans* (1), *C. guillermondii* (2)	5 (2)	32.5 (13)
p=NS		NA	NA
12.0 (2)	*C. albicans* (1), *Aspergillus* sp (1)	NA	17.6 (3)[j]
28.0 (5)	*C. tropicals* (1), *Curvularia* sp (1), *Cladosporium* sp (1), *Coccidioides* sp (1)	NA	50.0 (9)[j]
p=0.4			p=0.097
0 (0)	None	1.4 (1)[k]	15 (11)
2.3 (2)	*Candida* sp (2)	1.1 (1)[k]	14 (12)
p=NS		NA	NA
4 (10)[l]	IPA (10)[k]	1.3 (3)[m]	13.2 (30)
7 (11)[l]	IPA (11)[k]	1.3 (2)[m]	9.7 (15)
p=0.37		NA	NA
1.9 (3)	*C. albicans* (8), *C. glabrata* (1), *C. parapsilosis* (2), *Aspergillus* sp (1)	1.3 (2)	11.9 (19)
2.6 (5)	*C. albicans* (2), *C. glabrata* (2), *C. parapsilosis* (1), *C. krusei* (1), *Aspergillus* sp + *C. glabrata* (1), *Aspergillus* sp + *C. krusei* (1)	2.6 (5)	12.2. (24)
p>0.05		p>0.05	p>0.05
12.8 (11)	*C. albicans* (2), *C. parapsilosis* (2), *Candida* sp (2), *Aspergillus* sp (2), others (3)	7 (6)	29.1 (25)
12.0 (12)	*C. parapsilosis* (6), *C. tropicalis* (2), *C. glabrata* (1), *C. krusei* (1), *Aspergillus* sp (1), other (1)	6 (6)	22.0 (22)
NA		NA	NA
4.6 (5)[n]	*C. albicans* (1), *C. tropicalis* (1), *C. krusei* (1), *A. fumigatus* (2)	1.8 (2)	3.7 (4)
20.2 (22)[n]	*C. albicans* (2), *C. glabrata* (1), *C. tropicalis* (3), *A. fumigatus* (3)	7.3 (8)	8.2 (9)
p<0.01		p=0.07	p=0.13
4 (6)[o]	IPA[n] (6)	3.6 (5)	NA
14 (18)[o]	IPA[n] (18), *Fusarium* sp (1)	4.5 (6)	NA
p=0.005		p=0.8	
1.6 (7)[n]	*C. albicans* (1), *C. glabrata* (1), *C. parapsilosis* (1), *C. lusitaniae* (1), probable aspergillosis (1), Zygomycetes (1), *Fusarium* sp (1)	0.2 (1)	4.2 (18)
2.4 (11)[n]	*C. parapsilosis* (1), *C. krusei* (1), proven aspergillosis (4), probable aspergillosis (3),	0.4 (2)	5.7 (26)
p=0.481	*Fusarium* sp (2)	NA	p=0.322
5.3 (16)[n]	*C. glabrata* (1), *Trichosporon beigelii* (1), probable IPA (3), *Pseudallescheria boydii* (1), mould not specified (1)	0.7 (2)[n]	19.3 (58)
9.0 (27)[n]	*C. albicans* (1), *C. glabrata* (1), *C. krusei* (1), *A. fumigatus* (6), *A. flavus* (2), *A. terreus* (1),	3.8 (11)[n]	19.7 (59)
p=0.07	*Aspergillus* sp (4), probable IPA (4), Zygomycetes (1), mould not specified (1)	p=0.046	NA
11.6 (13)[q]	*Candida* sp (3), *Aspergillus* sp (7), Zygomycetes (2), other (1)	NA	NA
13.1 (23)[q]	*Candida* sp (3), *Aspergillus* sp (16), Zygomycetes (3), other (1)	NA	NA
p=0.5			

IFI = invasive fungal infection; BMT = bone marrow transplant; ANC = absolute neutrophil count; HM = hematologic malignancy; NA = not available; HSCT = hematopoietic stem cell transplant; GVHD = graft-versus-host disease; NR = not reported; L = liposomal; NS = not statistically significant; IPA = invasive pulmonary aspergillosis.

[a]Overall mortality at 90 days after transplantation.
[b]Proven, probable, and possible IFIs.
[c]Overall mortality at 110 days after transplantation.
[d]IFIs occurring within 50 days of BMT.
[e]Did not report in which maintenance group patients were enrolled.
[f]Documented as "per episode" since some patients entered into the study more than once.
[g]Microbiologically and clinically documented IFIs.
[h]If not specified as BMT or peripheral blood stem cell transplant, included as HSCT, with autologous or allogeneic if specified.
[i]Proven and suspected IFIs.
[j]Overall mortality at 1-yr follow-up.
[k]Mortality from proven and possible IFIs.
[l]Includes proven, probable, and possible IPA.
[m]Mortality from proven and probable IPA.
[n]Proven and probable invasive mould infections and candidemia.
[o]Includes proven and probable IPA.
[p]Prophylaxis was continued until day 180 after transplantation in patients who received prednisone ≥ 1 mg/kg/day or a T-cell–depleted HSCT.
[q]Proven, probable, and presumptive IFI rate at 12 mo.

adequate test of prophylaxis versus *Aspergillus* species. The rate of IFIs in fluconazole-treated patients was higher than that reported in previous studies[2, 3, 47–49, 52, 61] that evaluated fluconazole prophylaxis, perhaps because the fluconazole group included more patients with matched unrelated donor HSCTs, acute GVHD (grades II–IV), and chronic GVHD than in the itraconazole group, potentially biasing this study in favor of itraconazole.

In light of itraconazole's additional mould coverage, it was hoped that significant differences would be seen in terms of IMIs. However, thus far, the potential benefit has been demonstrated only in high-risk patient populations. The two studies that included only allogeneic HSCT recipients[36, 37] were able to demonstrate a significant decrease in IFIs; however, only one of the studies[37] was able to demonstrate a difference in IMIs (5% vs 12% itraconazole vs fluconazole groups, p=0.03), most likely because patients in the study were at very high risk for IMIs. Approximately half of the patients in each group had received HSCTs with unmatched related donors or matched unrelated donors, and about 80% of the patients in each group had acute grades II–IV GVHD. By contrast, in the five studies composed mainly of patients with hematologic malignancies or autologous HSCT recipients, no benefit was demonstrated.[45, 50, 57, 62, 63]

A benefit in terms of deaths due to IFIs or overall mortality was not observed in any of the seven itraconazole prophylaxis trials. Furthermore, in three studies, significantly more adverse effects (especially gastrointestinal complaints), laboratory abnormalities, and withdrawals due to adverse effects were noted in the itraconazole than in the fluconazole group.[36, 37, 57] In each of these studies, oral itraconazole solution was used; mean itraconazole concentrations (which were not measured in all patients) were greater than 0.5 µg/ml. In addition, patients receiving concurrent cyclophosphamide therapy with itraconazole exposes patients to higher concentrations of acrolein (a toxic metabolite of cyclophosphamide) compared with patients receiving fluconazole.[37, 68]

Breakthrough IFIs with both itraconazole-susceptible (*Aspergillus* species) and itraconazole-resistant (*C. krusei, C. tropicalis,* and *C. glabrata*) isolates have occurred in patients receiving itraconazole prophylaxis.

As there is conflicting evidence about the utility of itraconazole for prophylaxis, clinicians must make the decision to use this agent based on each individual patient's risk for IMIs. The benefit of using a mould-active agent was seen in two studies,[36, 37] one of which showed a benefit in terms of IFIs and one in terms of IMIs. Both of these studies included allogeneic HSCT recipients, and some patients had received unmatched related donor or matched unrelated donor HSCTs and had evidence of GVHD—all factors that increase the risk for IMIs. Thus, allogeneic HSCT recipients should receive prophylaxis with mould-active agents in the presence of other risk factors for IMIs such as unmatched related donor or matched unrelated donor HSCTs, GVHD, and immunosuppressive therapy. Perhaps the most important issue that would need to be addressed with the patient is adherence to the agent, as there are significantly more adverse effects with itraconazole than with fluconazole.

Amphotericin B

Amphotericin B has been investigated as a prophylactic agent in nine studies, primarily because of its broad-spectrum activity against *Candida* species, *Aspergillus* species, and Zygomycetes.[51, 53, 54, 56, 58–60, 64, 66] Varying doses, dosing schedules (every day or every other day), formulations (conventional, lipid), and routes of administration (oral, intravenous, aerosolized) have been evaluated. In all but two studies,[51, 56] amphotericin B was compared with placebo or no prophylaxis. In only one study,[54] however, was a decrease in the rate of IFIs observed; similarly, only one study[60] demonstrated a significant benefit in overall mortality.

Despite the use of higher intravenous doses of amphotericin B 0.2 mg/kg/day than had been used in trials comparing it with placebo, studies comparing conventional amphotericin B with fluconazole 200 or 400 mg/day failed to demonstrate a difference in rates of IFIs, mortality due to IFIs, or overall mortality.[51, 56] However, this dose is considerably lower than that recommended for treatment, which may have contributed to its inability to demonstrate impressive efficacy. Furthermore, patients in the amphotericin B groups experienced increased rates of renal toxicity compared with those in the fluconazole groups.

Finally, the use of inhaled amphotericin B has been studied for prophylaxis in order to limit the systemic toxicities of the drug. Aerosolized conventional amphotericin B provided no benefit over no aerosolized prophylaxis in terms of the cumulative incidence of proven, probable, or

possible invasive pulmonary aspergillosis.[58] In contrast, prophylaxis with inhaled liposomal amphotericin B decreased the frequency of invasive pulmonary aspergillosis compared with placebo (all patients also received fluconazole prophylaxis).[66] Differences in efficacy between formulations may be a result of the aerosol delivery systems used, their pulmonary pharmacokinetics, or that the liposomal carrier exhibits a pulmonary surfactant-like function whereas the deoxycholate formulation impairs surfactant function. However, the technical aspects of the administration and adverse effects of inhaled amphotericin B have yet to be refined. Thirty-one percent of patients discontinued the inhaled conventional amphotericin B, with 55% discontinuing due to adverse effects (cough, nausea, dizziness, tightness in the chest), 30% due to the inability to cooperate, and 4% because of noncompliance.[58] Also, more patients discontinued the inhaled liposomal amphotericin B than placebo (45% vs 30%, p=0.01) because they either could not use the nebulizer properly, had technical problems, or experienced coughing during inhalation.[66]

Breakthrough IFIs that occurred in the amphotericin B prophylaxis trials are listed in Table 2. None of the studies evaluated susceptibilities to amphotericin B or comparators. The increased risk of toxicity with conventional amphotericin B, high cost of liposomal amphotericin B, and equivocal results from trials preclude its routine use as a prophylactic strategy, and more studies are needed to access the efficacy of aerosolized amphotericin B for prophylaxis.

Micafungin

Despite their availability in only intravenous formulations, the echinocandins are of interest for prophylaxis (especially for patients who are intolerant of or allergic to azoles or who are receiving coadministration of immunosuppressive agents) because they display fewer drug interactions (compared with the azoles) and they are generally well tolerated. In addition, they have a broad spectrum of activity, which includes *Candida* and *Aspergillus* species (but not Zygomycetes or *Cryptococcus neoformans*). However, to our knowledge, micafungin is the only echinocandin that has been studied in a randomized controlled trial for prophylaxis in adult HSCT recipients.[46]

In this study, autologous and allogeneic HSCT recipients were randomly assigned to prophylaxis with either intravenous micafungin 50 mg/day or intravenous fluconazole 400 mg/day.[46] Micafungin was superior in terms of treatment success (defined as the composite end point of absence of a proven, probable, or suspected IFI at the end of prophylaxis and the absence of proven or probable IFI at the end of the 4-week post-prophylaxis period) compared with fluconazole (80% micafungin, 73.5% fluconazole, p=0.03). However, the rates of proven and probable IFIs, breakthrough aspergillosis, breakthrough candidiasis, adverse effects, discontinuation due to adverse effects, deaths due to IFIs, and overall mortality were similar between groups. Antifungal susceptibilities were not evaluated in this trial. Thus, this study validated that micafungin was as effective as fluconazole as a prophylactic agent in HSCT recipients and can be used as an alternative in azole-intolerant patients. However, a major limitation of this study was the relatively short duration of prophylaxis, which did not allow assessment of the efficacy of micafungin for prophylaxis in the postengraftment and late-phase high-risk periods for infections.

Voriconazole and Posaconazole

The recent availability of extended-spectrum azole antifungal agents, such as voriconazole and posaconazole, has led clinicians to inquire whether these agents may be superior prophylactic agents compared with fluconazole or itraconazole in HSCT recipients. Voriconazole has activity against *Candida* and *Aspergillus* species and is available orally and intravenously. Posaconazole has a similar spectrum of activity that also includes the Zygomycetes; however, it is only available orally.

Voriconazole was studied for prophylaxis in allogeneic HSCT recipients.[65] On day 0 (day of transplantation), patients were randomly assigned to receive either voriconazole or fluconazole intravenously or orally up to day 100, or day 180 if they received a T-cell–depleted HSCT or were receiving 1 mg/kg/day or more of prednisone. The study, which was powered to detect a 10% difference in fungal-free survival (freedom from proven or probable IFI or death at 6 mo), found no significant difference in fungal-free survival or in the cumulative rates of proven, probable, and presumptive IFIs or in overall mortality. Although the difference was not statistically significant, fewer patients in the voriconazole group developed microbiologically

documented infections due to *Aspergillus* species (voriconazole 7 vs fluconazole 16, p=0.05). These preliminary results, available only in abstract form, suggest that voriconazole provides no benefit over fluconazole in allogeneic HSCT recipients.

Posaconazole was compared with fluconazole in allogeneic HSCT recipients (at any time after HSCT) with acute grades II–IV GVHD or chronic GVHD while receiving immunosuppressive regimens.[55] Patients were randomly assigned to receive one of the azoles orally for a fixed treatment period of 112 days. Posaconazole was noninferior (and not superior) to fluconazole in terms of the primary end point, which was the frequency of proven or probable IFIs at the end of the 112-day treatment period, in the intent-to-treat population (fluconazole 9%, posaconazole 5.3%, p=0.07). However, at the end of the 112-day treatment period, posaconazole recipients had fewer IFIs due to *Aspergillus* species (fluconazole 7%, posaconazole 2.3%, p=0.006). Further, posaconazole recipients had fewer total breakthrough IFIs during the exposure period (day of first study drug dose until 7 days after receipt of the last study drug dose; fluconazole 8%, posaconazole 2%, p=0.004) and fewer breakthrough IFIs due to *Aspergillus* species during the exposure period (fluconazole 6%, posaconazole 1%, p=0.001). Fewer deaths due to proven or probable IFIs occurred in the posaconazole group, although there was no significant difference in overall mortality between the groups.

This study is a good example of targeting prophylaxis to a very specific group of patients at high risk for IFIs. Although posaconazole was not superior to fluconazole for the primary end point, it was shown to be noninferior to fluconazole and did decrease the number of deaths due to IFIs. It is important to note that the study did not address when mould prophylaxis should be started after transplantation. Although randomization occurred at various time points after transplantation, most patients were randomized more than 101 or between 30 and 60 days after transplantation and many patients had received fluconazole for antifungal prophylaxis before entering into the study. As the benefit of posaconazole prophylaxis has only been seen in a very specific subgroup of HSCT recipients who should be considered very high risk patients, potential patients should be evaluated for their risk factors for IFIs, ability to take oral drugs, ability to eat a fatty meal, and potential for drug-drug interactions before starting posaconazole prophylaxis.

A limitation to the above posaconazole and voriconazole studies is that the comparator, fluconazole, does not have any mould coverage. Two studies comparing voriconazole with itraconazole in allogeneic HSCT recipients will address this issue.[69, 70] Preliminary results from the first study, which evaluated open-label primary prophylaxis with either voriconazole or itraconazole for up to 180 days after transplantation, found that prophylactic success was significantly higher with voriconazole than with itraconazole at 100 and 180 days, but there was no significant difference in survival at 180 days.[69] Unfortunately, as intravenous itraconazole is no longer commercially available, the results of these studies will be applicable only for patients able to tolerate oral formulations of itraconazole. Another key issue not addressed in the aforementioned studies that needs to be addressed in future studies is the monitoring of voriconazole and posaconazole concentrations, as the oral bioavailability of these agents can be erratic. Wide interpatient variability in concentrations of gastrointestinal CYP enzymes, drug-drug and drug-disease interactions, and (for voriconazole) the presence of genetic polymorphisms in CYP2C19, contribute to the wide variability in plasma concentrations observed for these agents.[33, 34, 39, 41, 42, 44]

Cost-effectiveness studies in this population are limited; however, a recent study concluded that posaconazole is a cost-effective strategy for the prevention of IFIs in patients with GVHD, with an estimated incremental cost-effectiveness (vs fluconazole) of $15,700/life-year saved, and an 88% probability at a $50,000/life-year saved threshold.[71]

Conclusion

It is important to target antifungal prophylaxis by type of HSCT (autologous or allogeneic), local epidemiology, and risk factors for IFIs so that patients can receive the most appropriate agent while balancing costs and the risks of toxicity, and minimizing the development of resistance. Based on the literature reviewed, fluconazole still remains the gold standard for prophylaxis in autologous and most allogeneic HSCT recipients during the pre- and postengraftment period. Itraconazole and micafungin are alternative agents that may also be used in this population. The subgroup of allogeneic HSCT recipients with

severe GVHD benefit from the expanded mould coverage of posaconazole. However, the optimal times to begin and discontinue mould prophylaxis in this subgroup remain unknown. Despite numerous studies, the question of whether antifungal prophylaxis decreases mortality (either all-cause or due to IFIs) has yet to be definitively proven, and the optimal duration of antifungal prophylaxis needs to be determined. It is unclear whether *Candida* coverage with fluconazole should be administered during the pre- and postengraftment periods, followed by mould coverage during the late phase in high-risk patients, versus beginning administration of mould-active therapy in the preengraftment period and continuing it through the late phase. The potential benefits of antifungal prophylaxis depend on the basal rate of fungal infections; if there is a very low rate of *Aspergillus* infections in an institution, prophylaxis with mould-active agents is likely not warranted.

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