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REVIEW ARTICLE

Approaches to the Management of Invasive Fungal Infections in Hematologic Malignancy and Hematopoietic Cell Transplantation

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ABSTRACT

Patients with hematologic malignancy and hematopoietic cell transplant (HCT) recipients are at increased risk for invasive fungal infection (IFI) as a result of immunosuppression or organ damage stemming from their underlying disease, its treatment, or both. Such IFIs can cause significant morbidity and mortality, and the diagnosis and treatment of infected patients frequently are clinically challenging. This article discusses the epidemiology and risk factors for IFI in patients with hematologic malignancy and HCT recipients. The pros and cons of available antifungal agents are discussed, and evolving treatment strategies and recent prophylaxis guidelines from various professional organizations are reviewed. Finally, recommendations are offered for antifungal prophylaxis according to risk group.

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INTRODUCTION

The incidence of invasive fungal infection (IFI) in cancer patients has increased in recent years,[1] particularly in patients with acute leukemia and those undergoing allogeneic hematopoietic cell transplantation (HCT).[2] This increase in IFI is rooted in changes in treatment practices, including the use of more intensive chemotherapy; shifts in hematopoietic stem cell sources from related to unrelated donors and from bone marrow to HLA-matched or mismatched, peripheral, and umbilical cord stem cells; multiple transplantations; and transplantation with T-cell depletion.[1,3,4]

IFI is associated with significant morbidity and mortality[5,6] and can cause delays in or cancellation of treatment of the underlying disorder.[7] Although several new antifungal agents are available, treatment of established IFI is clinically challenging, and diagnosis remains difficult. Clinicians realized early that therapy could not be delayed until cultural or histologic diagnosis, and management strategies rapidly evolved from directed (specific) treatment to empiric and prophylactic approaches in patients at highest risk. Recently, a preemptive approach on the basis of radiographic and serologic criteria has been proposed for patients most likely to have IFI.[8]

EPIDEMIOLOGY

Candida and *Aspergillus* species are the leading IFI causes in patients with hematologic malignancy. However, epidemiology has shifted with the adoption of antifungal prophylaxis at many cancer centers. Previously rare pathogens such as *Fusarium* species and the Zygomycetes have emerged, whereas invasive candidiasis (IC) has decreased, occurring in less than 5% of HCT recipients and patients with acute myelogenous leukemia (AML) or acute lymphocytic leukemia (ALL).[2,9,10]

Candida albicans is the most common cause of IC, although other *Candida* species are emerging, including those with reduced antifungal susceptibility (eg, azole- and echinocandin-resistant *C glabrata*, *C parapsilosis*, and *C albicans*).[11,12,13] At a large US cancer center, *C glabrata* and *C krusei* caused candidemia in 31% and 24%, respectively, of patients with hematologic malignancy.[14] The Transplant-Associated Infection Surveillance Network (TRANSNET), a collaboration among the US Centers for Disease Control and Prevention, the University of Alabama at Birmingham, and 25 US transplant centers, reported that *C glabrata* now accounts for 32% of infections, whereas *C albicans* accounts for only 22% of infections.[15] The emergence of non-*albicans Candida* species is probably attributable to increased prophylactic use of azoles and widespread use of antifungal agents for febrile neutropenia.[16] The emergence of echinocandin-resistant *C albicans* in patients receiving prolonged echinocandin treatment also has been noted.[17]

Invasive aspergillosis (IA) occurs in an estimated 10% to 20% of allogeneic HCT recipients, in 10% of AML patients, in approximately 5% of ALL

patients, and in up to 2% of autologous HCT recipients.[2] IA incidence increased in the 1990s,[10] and, from 2001 to mid-2005 in the transplant population, seemed to stabilize at approximately 20 cases per 1,000 transplants.[15] However, in the second half of 2005, incidence rose sharply, reaching approximately 40 cases per 1,000 transplants.[15] Zygomycosis occurrence increased from 1.7 per 1,000 HCTs in 2001 to 6.2 per 1,000 HCTs in 2004.[18] By early 2006, Zygomycete infection accounted for approximately 25% of all IFIs in the transplant population.[15] The increase in zygomycoses, with the concomitant stabilization or decrease in IA, was attributed to prolonged use (eg, as prophylaxis or treatment) of voriconazole, an antifungal active against *Aspergillus* but not the Zygomycetes.[18,19]

In HCT recipients, a bimodal occurrence of IA after transplantation has been observed, with early (pre-engraftment, median 16 days after transplant) and late (postengraftment, median 96 days after transplant) peaks.[20] Late-onset IA occurs most often,[3,21] especially 90 or more days after transplant, when patients are out of the protected hospital environment and perhaps noncompliant with or inadequately absorbing oral antifungal prophylaxis.[22,23] IA-attributable mortality is high: approximately 50% in patients with leukemia and lymphoma and 87% in bone marrow transplant recipients.[5] However, survival improved recently, as reflected in TRANSNET data, which showed a 42% survival rate 3 months after IA in HCT from 2001 to 2006.[15] This might be due, partly, to availability of more effective antifungal therapy.[24] Finally, although *Aspergillus fumigatus* is the most common IA cause,[10] IA caused by non-*fumigatus Aspergillus* has recently increased.[10,25,26]

Fusarium and *Scedosporium* species have also emerged as important etiologic agents.[10,27,28] Fusariosis incidence increased by 40% from 1992 to 1999 at the Fred Hutchinson Cancer Research Center (Seattle, WA),[10] whereas an overall incidence of 5.97 cases of fusariosis per 1,000 HCTs were reported at nine US and Brazilian hospitals between 1985 and 2001.[29] Both are associated with poor outcomes: mortality rates of 53% to approximately 80% have been reported for fusariosis,[30,31] whereas a 100% fatality rate has been reported with scedosporiosis.[10]

RISK FACTORS

In general, the likelihood of IFI depends on the patient's state of immunocompetency, degree of organ damage (eg, mucositis, graft-versus-host disease [GVHD]), and microbial exposure (ie, colonization, environment, and prior infection), factors that are confounding and interrelated.[2] Neutropenia is a major risk factor for patients undergoing remission-induction chemotherapy and for HCT recipients during the early, pre-engraftment period.[32,33] IFI risk increases with neutropenia duration and severity; an absolute neutrophil count of 100 to less than 500 cells/mm^3 lasting for less than 3 weeks imparts moderate risk, whereas $\geq$ 5 weeks of neutropenia with an absolute neutrophil count of less than 500 cells/mm^3 imparts high risk.[34] The chemotherapy agent (ie, high-dose cytarabine) or protocol used and the leukemia subtype (particularly M0) in AML patients are also risk factors.[7] Other risk factors relating to immunosuppression include older age and, in leukemia, the underlying disorder (ie, abnormal circulating peripheral neutrophils).[33,35] In addition, the use of infliximab results in an increased frequency of IFIs.[36]

Specific pathogens are associated with certain risk factors. In HCT recipients after engraftment, GVHD and its treatment (ie, corticosteroids), especially if prolonged, and neutropenia are also important risk factors for IFI, particularly IA.[3,21] A retrospective analysis of 395 patients undergoing allogeneic peripheral stem cell transplantation between 1996 and 2000 showed that the strongest IFI risk factor was moderate to severe GVHD, whereas steroid use doubled the risk.[21] Another study of allogeneic HCT recipients between 1993 and 1998 showed that higher steroid doses used for GVHD increased IA probability at $\geq$ 40 days after transplant; 2 to 3 mg/kg/d and more than 3 mg/kg/d were associated with hazard ratios of 8.0 and 15.4, respectively.[3] In addition, a relationship exists between the level of IA risk and the degree of donor/recipient mismatch (ie, mismatched > unrelated > related > autologous). IA has also been reported in HCT recipients receiving antithymocyte globulin and patients receiving alemtuzumab for refractory lymphoproliferative disorders.[37,38]

IC is often related to a breakdown in mucosal integrity caused by chemotherapy, radiation, gut GVHD, an indwelling catheter, or prior surgery.[33,35,39] This disruption provides colonizing yeast access to the bloodstream.[33,39] Other IC risk factors include bacteremia, prior exposure to broad-spectrum antimicrobial agents, neutropenia, and corticosteroid use.[35,40]

MANAGEMENT STRATEGIES

Early diagnosis and prompt IFI treatment improve patient outcome. However, diagnosis is difficult because IFI symptoms are nonspecific and often indistinguishable from those of bacterial or viral infection.[41] Microbiologic culture techniques typically have low sensitivity for detecting mold infection.[42] Newer techniques include the serum galactomannan assay for *Aspergillus*, the serum (1,3)-β-D-glucan antigen test, and polymerase chain reaction assays.[42-45] The galactomannan assay has been studied most extensively, but false-negative results are common, especially in patients already receiving mold-active agents.[46] This makes the test less useful in HCT and neutropenic AML and myelodysplastic syndrome (MDS) settings, in which most patients receive prophylaxis. The β-D-glucan test also has false-positive and false-negative results.[47,48] Polymerase chain reaction assay remains a research tool; there is no consistent, universally available assay.

General IFI management strategies include (1) directed treatment of established infections requiring microbiologic identification of the pathogen; (2) preemptive antifungal therapy for high-risk patients whose signs, symptoms, or test results (radiographic, serologic) are suggestive of IFI; (3) empiric therapy for at-risk (eg, neutropenic) patients with persistent fever despite broad-spectrum antibacterial therapy; and (4) prophylaxis, in which antifungal treatment is designed to prevent infection in an at-risk population. Because clinicians should not await identification of the pathogen before initiating therapy (untreated IFIs are rapidly fatal), directed therapy is useful for focusing antifungal therapy after one of the earlier approaches has been initiated. Prophylaxis is useful in high-risk groups (eg, HCT recipients or patients with prolonged neutropenia) in which benefits of treating the entire population outweigh risks. The IFI rate at which prophylaxis becomes justified is usually $\geq$ 10%.[49] Empiric therapy treats more patients (eg, febrile neutropenic) than actually have or will have IFI. To avoid unnecessary treatment, a preemptive approach has

also been suggested,[8] although reliable predictive tests do not exist for IFI.

AVAILABLE AGENTS AND THEIR USE IN DIRECTED THERAPY

Antifungal agents include polyenes, azoles, and echinocandins. They are discussed here in order of historical development. Indications, activity spectra, and toxicity profiles of these agents, as well as other considerations, are presented in Table 1.

The polyene amphotericin B deoxycholate has been a mainstay of antifungal therapy since its development in the 1950s.[50,73] Amphotericin B acts by increasing fungal cell membrane permeability through effects on membrane ergosterol. The agent is fungicidal, which is thought to be responsible for the lack of resistance after decades of use, and has a broad spectrum of activity.[51,55-60] Amphotericin B deoxycholate is associated with significant toxicity, particularly nephrotoxicity,[52] whereas lipid formulations, which became available in the 1990s, including a lipid complex, a colloidal dispersion (ABCD), and a liposomal formulation (L-AmB), have improved toxicity profiles. A recent review of studies concluded that there were no significant differences in nephrotoxicity between ABLC and L-AmB.[86] Open-label, retrospective, and randomized controlled studies have shown that lipid formulations are effective as first-line and salvage treatment for IA, candidiasis, fusariosis, and zygomycosis.[63,87-93] In addition, lipid formulations are also highly effective against dimorphic fungi, including endemic mycoses.[51]

Azoles, which first became available in the late 1950s,[73] act by inhibiting the cytochrome P450 (CYP) –dependent enzyme lanosterol demethylase (14-α-sterol demethylase), an enzyme critical for synthesis of fungal membrane ergosterol.[73] Because azoles inhibit elimination of a number of drugs by competition for the CYP isoenzyme CYP3A4, drug interactions are an important consideration for this antifungal class.[94] However, the degree of CYP3A4 inhibition, of interaction with other enzymes, and, ultimately, of potential for drug interactions varies among azoles.

Fluconazole, introduced in the United States in the early 1990s, is active against most yeasts but lacks antimold activity.[51,73] Its efficacy in successfully treating candidemia has been shown prospectively to be not statistically different from amphotericin B, ($P = .22$).[95] Fluconazole was followed by the development of itraconazole, also introduced in the United States in the early 1990s.[73] Itraconazole has in vitro activity against yeasts and some molds (eg, *Aspergillus* species, dimorphic fungi)[51] and has clinical efficacy against IA.[96,97] However, the drug interaction risk with itraconazole is high.[68] Furthermore, bioavailability of the oral capsule formulation is low, and administration to healthy volunteers produces wide variation in plasma concentrations.[68,69,98] Although the bioavailability of the oral solution is improved,[99,100] it is poorly tolerated.[67]

Caspofungin was the first echinocandin to receive US Food and Drug Administration (FDA) approval (2001),[101] followed by micafungin (2005) and anidulafungin (2006).[102,103] Echinocandins inhibit the β-1,3-D-glucan synthase enzyme complex in the fungal cell wall.[84] They are fungicidal for yeasts (ie, most *Candida* species) and fungistatic for molds (ie, *Aspergillus*).[84] Echinocandins exhibit poor oral bioavailability and, therefore, must be administered intravenously.[84] No evidence suggests differences in efficacy or toxicity among the echinocandins, which have not been associated with nephrotoxicity or hepatotoxicity. Efficacy of the echinocandins against candidemia has been shown in open-label and randomized controlled trials in populations that included HCT recipients and patients with malignancy.[104-106]

Voriconazole, an extended-spectrum triazole that became available in 2002,[107] has shown efficacy as primary or salvage therapy for IA and other IFIs in open-label, randomized, or noncomparative trials that included HCT recipients and patients with hematologic malignancy.[24,108,109] However, voriconazole lacks activity against the Zygomycetes, and breakthrough and life-threatening zygomycosis has been reported with its use.[19,89-92] The drug is available in a well-absorbed oral formulation and an intravenous formulation. Voriconazole penetrates CSF and brain, and outcomes in patients with CNS IFI suggest that therapeutic levels in the CNS are attainable.[110]

Posaconazole, also an extended-spectrum azole, received FDA approval in 2006 and is only available in an oral formulation. Compared with other azoles, posaconazole has a low drug interaction potential because it inhibits CYP3A4 only, and is neither a substrate nor inhibitor of other CYP enzymes.[82] Posaconazole has shown efficacy as salvage therapy against a broad spectrum of IFIs, including fusariosis, histoplasmosis, and zygomycosis,[111-115] and has been associated with a significantly higher overall success rate for IA than external contemporaneous controls ($P = .006$).[116] Specific recommendations for directed therapy on the basis of the authors' review of the literature and clinical experience are presented in Table 2.

EMPIRIC ANTIFUNGAL THERAPY

In neutropenic patients with cancer, empiric antifungal therapy is an option for those still febrile after 3 to 5 days of antibiotic therapy.[118] Amphotericin is effective as empiric therapy but is associated with significant toxicity.[119] L-AmB efficacy is similar to that of conventional amphotericin for empiric therapy but with fewer adverse events.[53,61]

The azoles have also been studied as empiric therapy. Fluconazole has shown comparable efficacy to amphotericin B for neutropenic fever in cancer patients.[120] However, the lack of antimold activity and the probability of already being administered as prophylaxis may preclude empiric fluconazole use. Itraconazole administered intravenously and then as an oral solution was as effective as, but less toxic than, conventional amphotericin in an open-label, randomized study in febrile neutropenic cancer patients.[121] In a similar, more recent study, itraconazole was discontinued significantly less often because of adverse events ($P < .0001$) and had a significantly ($P < .0001$) greater response rate than conventional amphotericin; however, trends toward a longer response time and greater number of febrile days were seen with itraconazole.[122] In a study in febrile neutropenic cancer patients, approximately half of whom underwent HCT, voriconazole was associated with significantly ($P = .02$) fewer breakthrough IFIs than L-AmB.[74] However, because the overall voriconazole success rate was lower than that of L-AmB, and because "noninferiority" was not demonstrated, voriconazole did not receive FDA approval as empiric therapy.[123] In a small, noncomparative posaconazole trial in patients with refractory IFI or febrile neutropenia, posaconazole showed efficacy as empiric therapy in both groups.[124]

Table 1. Directed Treatment of Established Fungal Infections

Agent	Indication*	Spectrum of Activity	Toxicity Profile and Other Considerations
Polyenes			
Amphotericin B deoxycholate	• Broad range of systemic fungal infections	• Broad spectrum of activity against molds (including *Aspergillus*, the Zygomycetes, dimorphic fungi) and yeasts[58]	Significant toxicity profile,[59,104,138] including • Nephrotoxicity • Infusion-related reactions • Hypokalemia
Amphotericin B lipid formulations	Varies by specific agent but includes • Empiric therapy for suspected fungal infection • Cryptococcal meningitis in HIV-infected patients • Treatment of patients with disease refractory to or who are intolerant of amphotericin B	• Less active against *Candida* lusitaniae, C guilliermondii, Scedosporium prolificans, S apiospermum, Trichosporon beigelii, *Aspergillus* terreus, and *Fusarium* (especially *F solani*)[52-57]	• Lower toxicity than deoxycholate formulation[103,104] • Variation in tolerability among lipid formulations[139] • ABCD formulation associated with more adverse events than conventional[66] • Reduced potential for nephrotoxicity compared with conventional formulation[138]
Azoles			
Fluconazole	• Vaginal, oropharyngeal, and esophageal candidiasis • Urinary tract infections • Systemic *Candida* infections • Cryptococcal meningitis (US); cryptococcosis including cryptococcal meningitis and infections of other sites (EU) • Prophylaxis for candidiasis	• Spectrum limited to yeast[58] • Reduced susceptibility of *C glabrata* and *C krusei*[140]	• Well tolerated[120,121] • Hepatotoxicity (rare) • Drug interactions
Itraconazole	• Blastomycosis (US only) • Histoplasmosis • Aspergillosis in patients with disease refractory to/intolerant of amphotericin B • Aspergillosis, candidiasis, and cryptococcosis, including cryptococcal meningitis (EU only)	• Broad spectrum of activity (ie, *Candida Cryptococcus*), dermatophytes, and some molds (eg, *Aspergillus*, dimorphic fungi)[58] • Resistance in *Candida* glabrata (46-53%) and *C krusei* (31%)[140] • Cross-resistance with fluconazole[141]	• Poor tolerance with oral solution[78] • Capsule formulation displays wide variability in plasma concentrations and low bioavailability; oral cyclodextrin solution is better absorbed than capsule[73,74] • Monitoring of serum levels recommended for oral formulations • Significant drug interactions[73] • Hepatotoxicity with cyclophosphamide[129,142]
Voriconazole	• IA (first line) • Esophageal candidiasis (US only) • Candidemia in nonneutropenic patients • Serious fluconazole-resistant invasive *Candida* infections (EU only). However, significant cross-resistance with fluconazole can occur • Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium*, in patients with disease refractory to/intolerant of other therapy	• Extended spectrum of activity[51] • Active against a variety of fungal pathogens, including *Candida*, *Aspergillus*, *Cryptococcus*, and dimorphic fungi (eg, *Blastomyces dermatitidis, Coccidioides immitis,* and *Histoplasma capsulatum*)[51,55] • Lacks activity against the Zygomycetes[55]	• Significant drug interactions with many agents (eg, sirolimus)[108,143] • Variable intersubject plasma concentrations[143] • Unusual adverse effect profile, including visual disturbances during infusion and hallucinations[108,143] • Cyclodextrin in intravenous formulation may accumulate and be nephrotoxic in patients with renal dysfunction[108,143] • Breakthrough zygomycosis has been reported[19,89-92]
Posaconazole	• Prophylaxis of IFIs (EU) or IA and IC (US) in HCT recipients with GVHD and patients with hematologic malignancy with prolonged neutropenia from chemotherapy • Oropharyngeal candidiasis, including infections refractory to itraconazole or fluconazole (US) or as first-line therapy for severe disease or in immunocompromised patients (EU) • Refractory IA, fusariosis, coccidioidomycosis (EU only)	• Extended spectrum of activity[55] • Active against most frequently isolated yeast and mold pathogens, including *Candida*, *Aspergillus*, *Cryptococcus*[55] • In contrast to voriconazole, active against the Zygomycetes and *Fusarium*, as well as *Candida* and *Aspergillus* isolates (including *A terreus*) that exhibit resistance to amphotericin B and other azoles[55]	• Safety profile generally comparable to that of fluconazole[132,133] • Lower potential for drug-drug interactions than voriconazole or itraconazole[94] • Oral formulation only • Bioavailability is significantly enhanced by concomitant ingestion of a high-fat meal, any meal, a nutritional supplement, a low pH beverage, or with 4× daily dosing[144]
Echinocandins			
Caspofungin	• Empiric therapy for presumed fungal infections • Candidemia and certain *Candida* infections, including esophageal candidiasis (US); treatment of IC (EU) • IA in patients with disease refractory to/intolerant of other therapy	• Active against *Aspergillus* and many *Candida*, some dimorphic molds such as *H capsulatum*, *C immitis*, and *B dermatitidis* (probably mycelial but not yeast forms)[82,143] • Less active against *C parapsilosis*, *C lusitaniae*, and *C guilliermondii*)[82,143] • Limited or no activity against *C neoformans*, *Trichosporon*, *Rhodotorula*, and molds such as *Fusarium*, *Scedosporium*, the Zygomycetes, *Pseudallescheria boydii*, and dematiaceous molds[82,143]	• Few drug interactions[82] • Drug interaction with cyclosporine[82] • Well tolerated[82] • Intravenous formulation only[82] • Does not achieve good urinary concentrations

(continued on following page)

Table 1. Directed Treatment of Established Fungal Infections (continued)

Agent	Indication*	Spectrum of Activity	Toxicity Profile and Other Considerations
Micafungin	• Treatment for esophageal candidiasis, candidemia, acute disseminated candidiasis, *Candida* peritonitis, and abscesses (US) • Prophylaxis of *Candida* infections in patients undergoing HCT (US)	• Active against *Candida* and *Aspergillus* • Little activity against *C neoformans*, *F solani*, *P boydii*, *Trichosporon*, and the Zygomycetes[82,143] • Active against the mycelial but not yeast forms of dimorphic fungi such as *H capsulatum*, *B dermatitidis*, and *C immitis*[145]	• Few drug interactions[82] • Well tolerated[82] • Intravenous formulation only[82] • Does not achieve good urinary concentrations
Anidulafungin	• Candidemia and other forms of *Candida* infections (US) • Esophageal candidiasis (US) • IC in adult nonneutropenic patients (EU)	• Active against *Candida*, *Aspergillus*, and dimorphic fungi (mycelial forms)[82,143] • Not active against *C neoformans*, the Zygomycetes, *Fusarium*, or *Trichosporon*[82,143]	• Few drug interactions[82] • Well tolerated[82] • Intravenous formulation only[82] • Does not achieve good urinary concentrations

Abbreviations: ABCD, amphotericin B colloidal dispersion; US, United States; EU, European Union; IA, invasive aspergillosis; IFI, invasive fungal infection; IC, invasive candidiasis; HCT, hematopoietic cell transplant; GVHD, graft-versus-host disease.

*Sources for indications: Amphocin (amphotericin B for injection, USP), Pfizer, New York, NY; Amphotec (amphotericin B cholesteryl sulfate complex for injection), Three Rivers Pharmaceuticals, Cranberry Township, PA; AmBisome (amphotericin B) liposome for injection, Fujisawa, Deerfield, IL; Abelcet (amphotericin B lipid complex injection), Enzon Pharmaceuticals, Piscataway, NJ; Diflucan (fluconazole tablets; fluconazole injection—for intravenous infusion only; fluconazole for oral suspension), Pfizer, New York, NY; Sporanox (itraconazole) oral solution, Ortho Biotech, Raritan, NJ; VFEND (voriconazole) for injection, VFEND (voriconazole) tablets, VFEND (voriconazole) for oral suspension, Pfizer, New York, NY; NOXAFIL (posaconazole) oral suspension, Schering-Plough, Kenilworth, NJ; Cancidas (caspofungin acetate) for injection, Merck, Whitehouse Station, NJ; Mycamine (micafungin sodium) for injection, IV infusion only, Astellas Pharma, Deerfield, IL; Eraxis (anidulafungin) for injection, Pfizer, New York, NY.

With regard to echinocandin empiric therapy, in a randomized, comparative trial of caspofungin versus L-AmB in cancer patients (< 10% HCT) with febrile neutropenia, the agents were comparable in overall response, breakthrough IFI, and resolution of fever during neutropenia, although caspofungin was superior for baseline infection resolution, survival through 7 days of follow-up, and discontinuations as a result of toxicity.[125] Specific recommendations for empiric therapy on the basis of the authors' literature review and clinical experience are presented in Table 3.

PREEMPTIVE THERAPY

Because of the relatively few studies that have compared empiric therapy with either placebo or no therapy, the epidemiologic shift from candidiasis to mold infections, and increased availability of mold-active agents for prophylaxis, the use of fever alone as a trigger for empiric therapy has been questioned.[126] Maertens et al proposed a protocol-driven preemptive approach in high-risk neutropenic patients that included diagnostic evaluation with well-defined clinical, radiologic, and microbiologic criteria.[8] Seropositive (positive *Aspergillus* galactomannan assay) patients and patients with a positive microbiologic test result plus supportive radiologic findings received L-AmB. The approach reduced antifungal use by 78% and led to early initiation of antifungal therapy in 10 episodes (7.3%) that were clinically not suspected of being IFI. Some centers have implemented this approach, arguing that only patients with pulmonary abnormalities consistent with IFI should be treated, thus avoiding unnecessary exposure that may occur with prophylaxis.[127] However, there are no

Table 2. Author Recommendations for Directed Therapy

Infection	Primary Therapy	Secondary or Salvage Therapy
Caused by		
Aspergillus species	Voriconazole	Lipid form AmB, posaconazole, itraconazole
Zygomycetes	Lipid form AmB	Posaconazole
Fusarium species	Lipid form AmB	Voriconazole, posaconazole
Scedosporium apiospermum	Voriconazole	Itraconazole
Scedosporium prolificans	Voriconazole	
Unknown mold	Lipid form AmB	Posaconazole, itraconazole, voriconazole
Mold infection breakthrough on		
Voriconazole prophylaxis	Lipid form AmB	Posaconazole
Echinocandin prophylaxis	Lipid form AmB	Voriconazole
Candidemia		
Unstable, resistance suspected*	Lipid form AmB, echinocandin	Voriconazole
Stable, resistance not suspected	Fluconazole	

NOTE: Some recommendations based on discussion in Nucci.[117] Primary and secondary recommendations are based upon a high level of evidence, but not necessarily the highest (prospective, randomized, double-blind) level of evidence.

Abbreviation: AmB, amphotericin B.

*If the patient has a recent history of therapy with echinocandin or azole, a lipid formulation of amphotericin B should be used initially. When the *Candida* species is identified and sensitivities are known, therapy can be switched to an echinocandin or azole.

Table 3. Author Recommendations for Empiric Therapy

Primary Therapy	Secondary Therapy
Caspofungin	Voriconazole
Liposomal AmB	Posaconazole
	Itraconazole*
	Fluconazole*
	Micafungin
	Anidulafungin

NOTE: Primary therapy refers to those drugs that are recommended first, since the evidence justifying their use is of the highest standard (ie, based upon prospective, controlled, usually double-blind studies). The evidence for secondary therapy drugs does not meet this standard and the recommendations are based on less rigorous trials, anecdotal reports, and expert opinion.
Abbreviation: AmB, amphotericin B.
*Not recommended if prophylaxis with fluconazole or itraconazole has already been administered.

adequate prospective studies to determine whether this approach is effective and safe (ie, will not result in missed patients) or which antifungal agent should be used. In addition, there have been problems with preemptive tests (eg, the high false-negative rates of the galactomannan test in patients receiving antifungal agents and some antibiotics) precluding its use in certain (eg, HCT) settings.

ANTIFUNGAL PROPHYLAXIS

In the 1980s, when amphotericin B deoxycholate was the only effective agent for IFIs, it was evaluated in low doses (5 to 10 mg/d) as prophylaxis in HCT recipients.[128] In this retrospective study, IFI incidence decreased from 30% in 1986 (15% aspergillosis; 15% candidemia) before routine prophylaxis to 9% (6% aspergillosis; 3% candidemia) with amphotericin B during 1987 through 1989 ($P = .0004$). Of the patients who developed candidemia in the later period, none received prophylaxis for a sufficient duration to reflect failure. No significant nephrotoxicity was suffered by those who received amphotericin B prophylaxis. However, recently, because of the viewpoint of some that amphotericin B deoxycholate should rarely be used[129] and the erratic supply of the drug, the conventional formulation is rarely used for prophylaxis; instead, lipid formulations have been used. In two placebo-controlled, double-blind, randomized studies of L-AmB in HCT recipients and in patients receiving chemotherapy, a trend

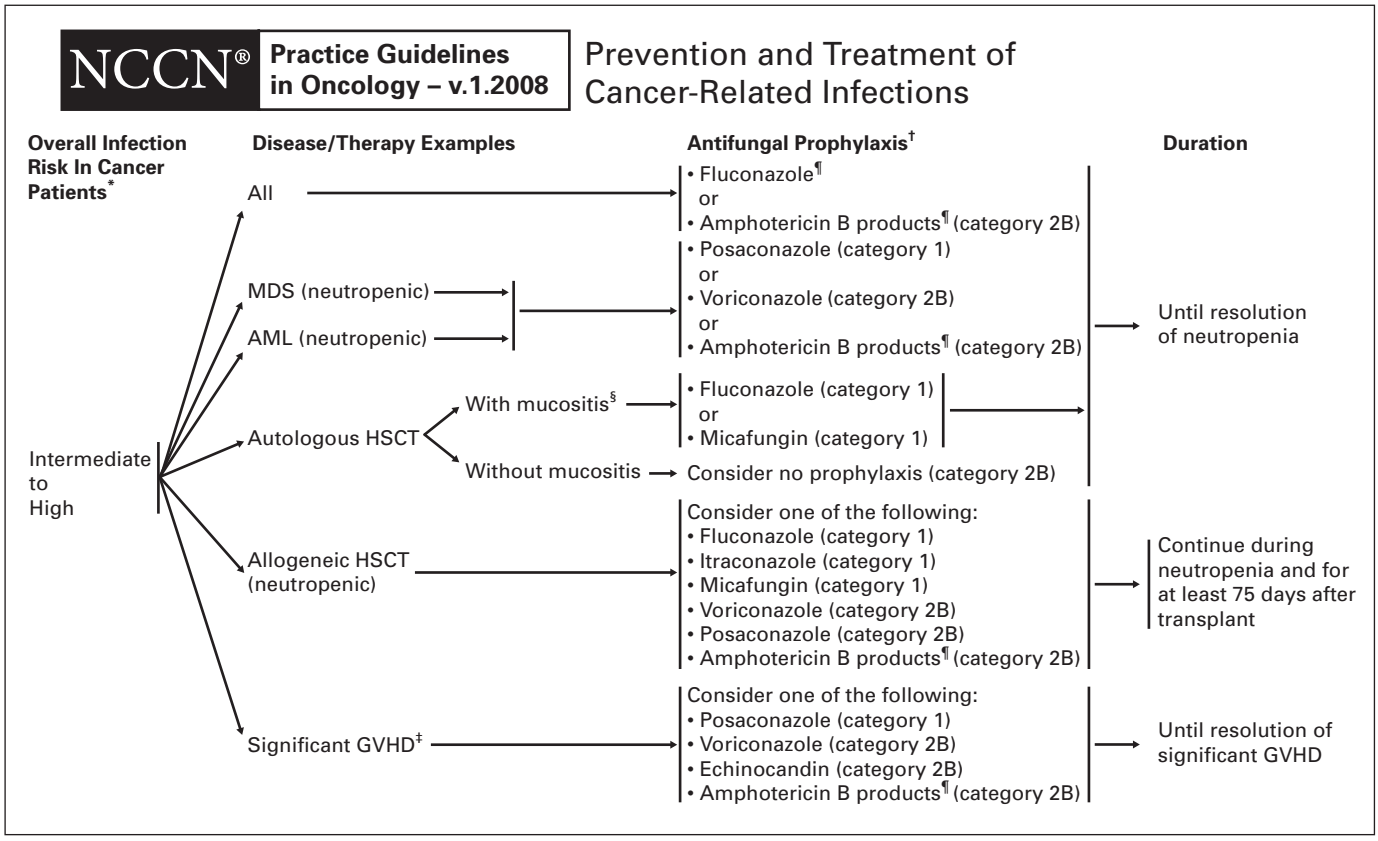

Fig 1. National Cancer Care Network recommendations for invasive fungal infection (IFI) prophylaxis in cancer patients as of February 2008 (reprinted with permission). Definitions of category ratings are as follows: 1 indicates uniform consensus, on the basis of high-level evidence, that the recommendation is appropriate; 2A indicates uniform consensus, on the basis of lower-level evidence, including clinical experience, that the recommendation is appropriate; 2B indicates nonuniform consensus (but no major disagreement), on the basis of lower-level evidence, including clinical experience, that the recommendation is appropriate; and 3 indicates major disagreement that the recommendation is appropriate. *General categories on the basis of duration of neutropenia, underlying disease, intensity of chemotherapy, and other immunomodulatory therapies. †See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions. ‡Consider antifungal prophylaxis in all patients with GVHD receiving immunosuppressive therapy. See Antifungal Prophylaxis section of this article. §Severe mucositis is a risk factor for candidemia in patients with hematologic malignancies and stem cell transplant recipients not receiving antifungal prophylaxis. ‖Itraconazole, voriconazole, and posaconazole are more potent inhibitors of hepatic cytochrome P450 A isoenzymes than fluconazole and may significantly decrease the clearance of vinca alkaloids. ¶A lipid formulation is generally preferred on the basis of less toxicity. MDS, myelodysplastic syndrome; AML, acute myelogenous leukemia; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease.

toward reduced IFI incidence was observed.[130,131] However, a randomized trial comparing fluconazole with ABCD was terminated prematurely because of severe infusion-related adverse effects with ABCD.[132] Preliminary results of a more recent randomized trial in patients with AML or MDS undergoing induction or salvage chemotherapy showed intermittent L-AmB (once or thrice weekly) was well tolerated and as effective as voriconazole twice daily in preventing IFIs.[133]

Two double-blind, placebo-controlled trials have shown that prophylactic fluconazole reduced morbidity and mortality rates among neutropenic HCT recipients.[64,65] In Goodman et al,[64] prophylactic fluconazole in autologous and allogeneic HCT recipients resulted in significantly fewer IFIs (2.8% *v* 15.8%; $P < .001$) and fewer fungal-related deaths (1 of 79 *v* 10 of 177; $P < .001$) than placebo. However, no overall mortality difference was seen.[64] In the study by Slavin et al,[65] in which most patients were allogeneic HCT recipients, greater survival probability ($P = .0044$) and significantly fewer IFIs occurred with fluconazole versus placebo (7% *v* 18%; $P = .004$). The major difference between the studies was that, in the Goodman et al[64] multicenter study, fluconazole was administered until engraftment, whereas in the Slavin et al[65] single-center study, prophylaxis was continued until day +75. The survival benefit is thought to be attributable to the longer duration of prophylaxis, and most experts agree that prophylaxis should be administered for at least 75 days after transplantation. In an 8-year follow-up of Slavin et al, fluconazole conferred a significant long-term reduction in candidiasis and improvement of survival rate.[134] A decreased rate of severe gut GVHD and persistent protection against candidiasis-related death, resulting in an increased overall survival rate long after prophylaxis ended, was also seen.[134] Because of these data, fluconazole prophylaxis is the standard of care for HCT recipients, despite its lack of antimold activity.

Fluconazole prophylaxis has led to the emergence of non-*albicans Candida* and molds, resulting in infections that are more difficult to treat.[135-138] Antifungal prophylaxis has been associated with microbial shifts in colonization; for example, patients who received fluconazole and micafungin experienced increases in colonizing *C glabrata* and *C albicans*, respectively.[139]

Addition of aerosolized liposomal amphotericin to prophylactic fluconazole may offset the latter's lack of antimold activity, especially in the lung. In a randomized controlled trial of 271 patients with 407 neutropenic episodes caused by chemotherapy or HCT, nebulized amphotericin twice weekly plus fluconazole was associated with a significantly lower incidence of proven or probable invasive pulmonary aspergillosis compared with placebo plus fluconazole (4% [6 of 139] *v* 14% [18 of 132]; $P = .005$).[140] Three patients in the amphotericin group occurred after inhalation therapy was discontinued. No between-group difference in mortality was observed; however, significantly more patients on amphotericin discontinued inhalation therapy versus placebo, most commonly because of patient weakness, technical problems with the aerosol system, or coughing during inhalation.

Itraconazole confers protection against invasive molds in high-risk patients, although, in large randomized studies, it provided no survival benefit versus fluconazole and was associated with a higher incidence of adverse events.[71,141] In a meta-analysis of prophylaxis trials, itraconazole was associated with a significant reduction in IFI incidence ($P = .002$) and IFI-related mortality ($P = .04$) but not overall mortality, benefits that were seen primarily with the oral or intravenous cyclodextrin solutions.[67] Itraconazole reduced the incidence of yeast infections, including those caused by non-*albicans Candida* species but not IA. However, in trials that compared the oral solution with fluconazole or oral amphotericin, itraconazole discontinuation rates were double those of the comparators ($P < .0001$).[67]

Table 4. Antifungal Prophylaxis in Patients With Leukemia: Second ECIL Recommendations[144]

Patient Population	Recommendation Level
Allogeneic HCT	
Fluconazole 400 mg daily IV/oral	AI*
Itraconazole 200 mg IV followed by oral solution 200 mg twice a day	BI*†‡
Posaconazole 200 mg three times a day, oral	AI*‡
Micafungin 50 mg daily IV	CI
Polyenes§ IV	CI
Induction chemotherapy acute leukemia	
Fluconazole 50-400 mg daily IV/oral	CI*
Itraconazole oral solution 2.5 mg/kg twice a day	CI*†‡
Posaconazole 200 mg three times a day, oral	AI*‡
Echinocandins IV	Insufficient data
Polyene§ IV	CI

Abbreviations: ECIL, European Conference on Infections in Leukemia; HCT, hematopoietic cell transplant; IV, intravenous; A, strong evidence for efficacy and substantial clinical benefit (strongly recommended); B, strong or moderate evidence for efficacy, but only limited clinical benefit (generally recommended); C, insufficient evidence for efficacy, or efficacy does not outweigh possible adverse consequences (eg, drug toxicity or interactions), or cost of chemoprophylaxis or alternative approaches (optional); I, evidence from at least one well-executed randomized, controlled trial.

*Azoles should not be used empirically in case of prior azole prophylaxis.

†May be limited by drug interactions and/or patient tolerability.

‡Monitoring of serum drug concentrations is recommended.

§Includes low doses of amphotericin B deoxycholate and lipid formulations of amphotericin B. The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI.

The echinocandins have also been evaluated as prophylaxis, although their intravenous administration route makes them less attractive for routine long-term outpatient prophylaxis. In a double-blind study in neutropenic HCT recipients, micafungin was superior to fluconazole on the basis of prespecified criteria that included the absence of a breakthrough fungal infection ($P = .03$) and the absence of empiric modification of the antifungal regimen because of neutropenic fever ($P = .024$).[139] The frequency of breakthrough candidemia was similar in both arms, but there was a trend toward fewer IA episodes in allogeneic HCT recipients receiving micafungin ($P = .07$). The study, however, included a large number (70%) of autologous and low-risk allogeneic transplants and did not address the prevention of late-onset IFIs. Survival rate and drug-related toxicity were similar in both arms. In an open-label comparative trial in 192 patients undergoing induction chemotherapy for hematologic malignancy, caspofungin also showed prophylaxis efficacy comparable to that of itraconazole with no significant differences in IFI rates, mortality rates, or adverse events between treatment groups.[142]

The efficacy of posaconazole as prophylaxis in high-risk patients is superior to that of conventional azoles.[80,81] In a randomized, double-blind trial involving 600 allogeneic HCT recipients with GVHD, posaconazole was associated with significantly fewer proven or probable breakthrough IFIs (2.4% *v* 7.6%; $P = .004$), particularly breakthrough IA (1.0% *v* 5.9%; $P = .001$), and fewer instances of IA

Table 5. Author Recommendations for Prophylaxis

At-Risk Population/Period	Primary	Secondary
Autologous HCT	Fluconazole* Micafungin†	
Allogeneic HCT		
Neutropenia (IV) through day +75 (orally)	Fluconazole*	Itraconazole§‡ Posaconazole§‖
Neutropenia (IV) through day +100 (orally)	Voriconazole§¶	Itraconazole§‡ Posaconazole§‖
Neutropenia (IV) through engraftment	Micafungin†	Low dose amphotericin product† Itraconazole§‡ Posaconazole§‖
Postengraftment, high-risk (GVHD, corticosteroids)	Posaconazole§	Voriconazole§¶ Itraconazole
AML/MDS		
Neutropenia	Posaconazole§	Low-dose amphotericin product† Echinocandin† Voriconazole§¶ Itraconazole‡§

NOTE: Primary therapy refers to those drugs that are recommended first, since the evidence justifying their use is of the highest standard (ie, based upon prospective, controlled, usually double-blind studies). The evidence for secondary therapy drugs does not meet this standard and the recommendations are based on less rigorous trials, anecdotal reports, and expert opinion.

Abbreviations: HCT, hematopoietic cell transplant; IV, intravenous; GVHD, graft-versus-host disease; AML, acute myeloblastic leukemia; MDS, myelodysplastic syndrome.

*Fluconazole is not active against molds.

†Will require transition from an IV to an orally administered antifungal agent to complete prophylaxis.

‡Itraconazole may have increased toxicity when used in a cyclophosphamide-containing conditioning regimen.

§Serum levels of posaconazole, voriconazole, and itraconazole should be determined after 1 week of initiating oral therapy with these oral agents.

‖Posaconazole has not been studied in the neutropenic pre-engraftment phase of HCT.

¶Voriconazole is not active against the Zygomycetes.

during the entire study period (2.3% *v* 7%; $P = .006$) than fluconazole.[81] Overall mortality rates did not differ. In another large, evaluator-blinded, randomized, controlled trial involving 602 patients with neutropenia resulting from induction-remission chemotherapy for AML/MDS, posaconazole was superior to fluconazole or itraconazole in preventing IFI and IA during treatment (2% *v* 8%, $P < .001$, and 1% *v* 7%, $P < .001$, respectively) and IFIs throughout the study (5% *v* 11%; $P = .003$); the agent was also associated with lower overall ($P = .048$) and IFI-related ($P = .01$) mortality.[80]

Preliminary results of a large, randomized, double-blind trial comparing voriconazole with fluconazole as prophylaxis in 600 allogeneic HCT recipients showed that cumulative rates of proven, probable, and presumptive IFIs were similar between treatment arms at 6 months (10.6% fluconazole *v* 6.6% voriconazole; $P = .11$) and at 12 months (13.1% *v* 11.6%; $P = .50$), as were fungal-free survival rates (76% *v* 78% at 6 months; 65% *v* 63% at 12 months).[143] Overall mortality rates did not differ between groups. The causes of IFI at 6 months for fluconazole versus voriconazole were *Aspergillus*, 16 (5.4%) versus seven (2.3%; $P = .05$); *Candida*, three versus three; the Zygomycetes, three versus two; and other causes, one versus one. Therefore, although there was a significant decrease in IA, an increase in survival rate was not achieved with voriconazole. The results of this study were consistent with the TRANSNET data.[15] The increase in the number of zygomycoses as a proportion of all mold infection could be attributed to the decrease in *Aspergillus* infections. Although the numbers were small, it did not seem that zygomycosis was selected by voriconazole, unless fluconazole and voriconazole both selected for the Zygomycetes.

In summary, fluconazole, when administered until day +75, is the first antifungal agent to provide a survival advantage (over placebo) in HCT recipients.[65] No other agent has shown a survival advantage over fluconazole in this population despite decreases in IA. This may be attributable to the low incidence of IA in the studies that evaluated other agents,[81,139,143] or to comparator toxicity. In contrast, in patients with AML or MDS, IFI rates and survival benefit with posaconazole have been superior to those of fluconazole and itraconazole.[80]

CHOOSING AN ANTIFUNGAL AGENT FOR PROPHYLAXIS

If efficacy is based on an agent's ability to decrease the incidence of IFI caused by both yeasts and molds, numerous choices exist in the HCT setting, although no drug meets all criteria, that is, broadest spectrum, minimal toxicity, and availability as an intravenous formulation during the neutropenic/mucositis phase and as a well-absorbed oral formulation later (especially in the outpatient setting) to day 75 after transplantation. Thus, the choices come down to using (1) a single agent such as voriconazole intravenously initially, then orally until day 100 after transplantation or until GVHD resolves, risking zygomycosis; (2) posaconazole, which would require oral administration during the neutropenic/mucositis preengraftment phase of HCT, a setting in which this drug has not been tested; or (3) a sequential combination beginning with an intravenous formulation (eg, a lipid formulation of amphotericin B or micafungin) and subsequently switching to an oral formulation (posaconazole, voriconazole, itraconazole, or fluconazole) on discharge from the hospital until day +75 or until GVHD resolves. Finally, it should be noted that no prophylactic antifungal agent has been shown to be superior to fluconazole for survival in

the HCT setting, and fluconazole is still considered a standard at centers that have low invasive mold infection rates (< 5%).

Clinical guidelines are available from several organizations, including European Conference on Infections in Leukemia,[144] the National Comprehensive Cancer Network (NCCN; Fig 1), and Infectious Diseases Society of America.[145] These evidence-based recommendations, which continue to evolve, rely on such items as questionnaires on European practices, literature reviews, and Centers for Disease Control and Prevention grading. The greatest weight is given to prospective, randomized trials and the least to observational or historical control-based trials. The NCCN guidelines are also based on clinical observation and indicate where there was nonuniform consensus or disagreement. Some important differences exist among the recommendations. European Conference on Infections in Leukemia (Table 4) gives the highest rating to fluconazole and posaconazole for prophylaxis in patients with leukemia with allogeneic HCT and to posaconazole for prophylaxis in patients with acute leukemia receiving induction chemotherapy. No recommendations are made for autologous HCT recipients. In contrast, the NCCN highly recommends prophylaxis with fluconazole, itraconazole, and micafungin for allogeneic HCT recipients with neutropenia; posaconazole for patients with significant GVHD and neutropenic AML and MDS patients; and fluconazole and micafungin for autologous HCT recipients with mucositis. The Infectious Diseases Society of America similarly recommends posaconazole as primary prophylaxis against IA for HCT recipients with GVHD and neutropenic patients with AML or MDS; intravenous or oral itraconazole and micafungin are recommended alternatives.[145]

On the basis of our clinical experience, examination of the literature, and various guidelines, we offer somewhat more finely tuned recommendations (Table 5), including the use of prophylaxis until at least day +75 to 100, and longer if the patient remains at high risk (ie, prescribed corticosteroids for GVHD) for IFI.

Because azoles, and now echinocandins, are used more frequently and for longer duration, the emergence of resistance becomes more of a concern and, ultimately, may reduce the effectiveness of these two families of antifungal agents. Therefore, IFI prevention and treatment must remain an evolving process that adapts to the emergence of new etiologic agents or resistant strains of common pathogens by developing new drugs with different mechanisms of action, going "back to the future" with the renewed use of polyenes (to which fungi have not yet exhibited resistance), or developing new immunologically based approaches such as vaccination.[146]

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