Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in patients with acute leukemia and in those who undergo allogeneic hematopoietic stem cell transplantation (HSCT). Effective prevention and early diagnosis of IFIs are important priorities. Four strategies for preventing and treating IFIs are 1) prophylaxis, 2) empiric antifungal therapy, 3) preemptive antifungal therapy, and 4) treatment of established fungal infections.

In the prophylactic mode, an antifungal agent is initiated at a period of high risk (e.g., during neutropenia) to prevent a fungal infection. Empiric antifungal therapy is defined as initiation or modification of an existing antifungal regimen based on persistent neutropenic fever (generally 4–7 days) that has no known source and is unresponsive to appropriate antibacterial agents. Preemptive therapy has no standard definition in mycology but generally refers to using CT scans (to detect early mold infections), laboratory markers, or both to stratify the likelihood of an IFI in a prespecified patient population (e.g., those with persistent neutropenic fever of unknown origin). When prespecified criteria are met, preemptive initiation or modification of antifungal therapy would be triggered in patients at high risk. Treatment of an established IFI requires either a proven or probable IFI as defined by the EORTC/Invasive Fungal Infections Cooperative Group and the Mycoses Study Group (MSG) consensus criteria.1 In practice, the distinction between prophylaxis and early treatment strategies might be blurred. In addition, prophylactic trials often}

**Broad-Spectrum Antifungal Prophylaxis in Patients With Cancer at High Risk for Invasive Mold Infections: Point**

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**Key Words**

Invasive fungal infection, prophylaxis, preemptive therapy, aspergillosis

**Abstract**

Invasive fungal infections (IFIs) are a leading cause of infection-related mortality in patients with acute leukemia and prolonged neutropenia and in allogeneic hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD). Although invasive candidiasis was the principal IFI predating fluconazole prophylaxis, invasive aspergillosis and other mold infections now cause most deaths from fungal infection in this patient population. The availability of broad-spectrum antifungal agents that can be safely administered over prolonged periods has stimulated interest in using mold-active prophylactic agents early as prophylaxis rather than later as therapy for suspected or documented IFIs. Two recent, prospective, randomized trials have shown a clear benefit of posaconazole prophylaxis in patients with myelodysplastic syndrome and acute myelogenous leukemia with prolonged neutropenia and in allogeneic HSCT recipients with severe GVHD. In contrast, the peer-reviewed published database on the strategy of preemptive antifungal therapy, in which yeast-active prophylaxis (fluconazole) or no antifungal prophylaxis is used initially and modifications are triggered by a combination of laboratory markers and chest CT scans, is currently limited to an open-label feasibility study. Does sufficient evidence currently exist that the net benefit of the preemptive approach is at least on a par with posaconazole prophylaxis in the specific patient groups that were studied? The authors believe not and that more research is needed before the preemptive strategy can be recommended. *(JNCCN 2008;6:175–182)*

Invasive fungal infections (IFIs) are a leading cause of infection-related mortality in patients with acute leukemia and in those who undergo allogeneic hematopoietic stem cell transplantation (HSCT). Effective prevention and early diagnosis of IFIs are important priorities. Four strategies for preventing and treating IFIs are 1) prophylaxis, 2) empiric antifungal therapy, 3) preemptive antifungal therapy, and 4) treatment of established fungal infections.

In the prophylactic mode, an antifungal agent is initiated at a period of high risk (e.g., during neutropenia) to prevent a fungal infection. Empiric antifungal therapy is defined as initiation or modification of an existing antifungal regimen based on persistent neutropenic fever (generally 4–7 days) that has no known source and is unresponsive to appropriate antibacterial agents. Preemptive therapy has no standard definition in mycology but generally refers to using CT scans (to detect early mold infections), laboratory markers, or both to stratify the likelihood of an IFI in a prespecified patient population (e.g., those with persistent neutropenic fever of unknown origin). When prespecified criteria are met, preemptive initiation or modification of antifungal therapy would be triggered in patients at high risk. Treatment of an established IFI requires either a proven or probable IFI as defined by the EORTC/Invasive Fungal Infections Cooperative Group and the Mycoses Study Group (MSG) consensus criteria.1 In practice, the distinction between prophylaxis and early treatment strategies might be blurred. In addition, prophylactic trials often
have strict exclusion criteria (e.g., patients with significant hepatic or renal impairment) that are designed to enhance safety but may also diminish the generalizability of results to real-world practice.

Both the empiric and preemptive strategies have the goal of treating a possible early IFI before it becomes clinically overt. The empiric approach relies on persistent neutropenic fever alone as a decision point to modify antifungal therapy; this approach is limited by the lack of specificity for undifferentiated neutropenic fever. The goal of the preemptive approach is to use diagnostic tools that are more specific for an IFI and thus may be better able to stratify the likelihood of an IFI in a patient at high risk. The authors recently argued that persistent neutropenic fever is nonspecific for an IFI and should not be used as the sole criterion for empiric modification of the antifungal regimen in a patient receiving mold-active prophylaxis. Potential benefits and gaps exist in knowledge related to the preemptive strategy discussed in this article. In the authors’ opinion, the current database supporting posaconazole as mold-active prophylaxis in patients at highest risk for IFIs is far more definitive and persuasive than the limited but encouraging database on the preemptive approach. The preemptive approach has potential value for targeting antifungal therapy to patients with a greater likelihood of having an IFI and avoiding unnecessary antifungal agents in patients with negative screening results. However, more research is needed before this approach should be adopted in clinical practice.

Principles of Prophylaxis and Early Treatment of Infectious Diseases

The authors have previously discussed principles for prophylaxis and early treatment of infectious diseases in patients who are immunocompromised. The basic premises are as follows:

- The greater the potential for an infection to cause significant morbidity or mortality, the greater the need for effective prophylaxis. Conversely, prophylaxis is not warranted for infections that are not serious or respond easily to therapy.
- The higher the incidence of infection within a given population, the more likely a prevention or early treatment strategy will be used.
- The safer the agent, the more likely it will be used in a large number of patients (e.g., as prophylaxis) in which only a minority would be expected to benefit, but very few would incur toxicity.
- The greater the likelihood that a given antimicrobial agent will select for resistant pathogens, the greater the need to target the agent to those at highest risk for infection.
- The better the methods for early detection of infection, the more willing clinicians are to withhold prophylaxis or to not modify the regimen with negative screening results.

A preemptive approach is limited by sensitivity and specificity of the methods used for early detection. If an early diagnostic fungal marker was available with a 100% sensitivity and specificity and became positive at least 7 days before clinical or radiologic signs of an IFI then a strong rationale would exist to use this marker in a preemptive strategy in patients at risk for an IFI and to abandon the prophylactic strategy. In this idealized scenario, only patients who need an antifungal agent would receive it, and the remainder would be spared the potential toxicity of unnecessary treatment. Even among patients at highest risk for an IFI (e.g., relapsed leukemia, allogeneic HSCT recipient with severe graft-versus-host disease [GVHD]), most will not develop an IFI. Therefore, development of preemptive strategies that avoid unnecessary antifungal treatment in most patients at high risk is an important goal that merits further evaluation in clinical trials.

Methods to Detect Early Invasive Mold Infection

A chest CT scan is far more sensitive than a chest radiograph in the early detection of invasive aspergillosis in patients with prolonged neutropenia. The NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections (in this issue, or to view the most recent version, please visit the NCCN Web site at www.nccn.org) advise a chest CT scan in patients experiencing 10 to 14 days of neutropenia and persistent or recurrent fever of unknown origin that is unresponsive to empiric antibacterial agents. The earliest sign of invasive mold infection is a nodule with or without a halo sign, a hazy alveolar infiltrate corresponding to alveolar hemorrhage that surrounds the consolidative lesion.

Laboratory assays that measure fungal constituents are being used as diagnostic adjuncts for IFIs and as
Fluconazole is limited by lack of specificity, which may account for the poor performance of the galactomannan assay. Several variables can affect the performance of the galactomannan assay, which may account for the differences in the results of prospective studies. The sensitivity of the assay is significantly reduced by concomitant mold-active antifungal agents. False-positive results may be more common in children and allogeneic HSCT recipients. Concomitant piperacillin/tazobactam causes false-negative galactomannan results.

The value of serum galactomannan as a surveillance tool requires further study. In the best scenario, prospective serial monitoring of galactomannan antigenemia in allogeneic HSCT recipients yielded positive predictive values (PPVs) and negative predictive values (NPVs) of 94.4% and 98.8%, respectively, and antigenemia preceded radiographic findings by more than a week in 80% of patients with invasive aspergillosis. In another study, the sensitivity was only 64.5% in cases of definite invasive aspergillosis. The PPV was poor when used as a surveillance tool in patients with persistent neutropenic fever (PPV = 7.1%) and in HSCT (mostly autologous) recipients (PPV = 10%). A recent meta-analysis showed that the galactomannan assay had a sensitivity of 70% and specificity of 89% for proven invasive aspergillosis, and that the accuracy of the test was variable among different patient populations. In populations with a prevalence of invasive aspergillosis of 5% to 10%, the expected PPV ranged between 23% and 53%, whereas the expected NPV ranged between 95% and 99%. The NPV seems to be excellent. However, an assay that always produces negative results will have an NPV of 90% to 95% when the prevalence of invasive aspergillosis is 5% to 10%. The lack of consistent results between different studies likely relates to different cut-off values for a positive result, differences in patient populations, and possibly practices involving use of mold-active prophylaxis.

Odabasi et al. evaluated the β-glucan assay (Glucatell assay, Associates of Cape Cod) as an early diagnostic marker for invasive fungal infections in patients with acute leukemia or myelodysplastic syndrome receiving antifungal prophylaxis. At least one serum sample was positive at a median of 10 days before clinical diagnosis in all patients with a proven or probable IFI including candidiasis, fusariosis, trichosporonosis, and aspergillosis. The NPV was 100% and specificity of the test was 90% for a single positive test result and at least 96% for 2 or more sequential positive results. Experience with the β-glucan assay in HSCT recipients is limited and requires additional study. False-positive β-glucan assays can result from surgical packing, intravenous immunoglobulin, intravenous amoxicillin-clavulanate, and potentially other antibiotics. Taken together, radiologic and laboratory-based tools are available to facilitate early diagnosis of IFIs. The laboratory markers have important limitations that must be considered in preemptive algorithms.

**Mold-Active Prophylaxis**

Randomized trials have shown inconsistent benefit of prophylactic fluconazole in preventing invasive candidiasis in patients with acute leukemia. Fluconazole prophylaxis was beneficial in HSCT recipients during neutropenia. Breakthrough candidemia, although uncommon, is well-reported in patients with cancer receiving fluconazole prophylaxis. In a meta-analysis of 16 randomized controlled trials in non-HSCT recipients with chemotherapy-induced neutropenia, fluconazole prophylaxis seemed to be effective when the incidence of systemic fungal infection was expected to be more than 15%. Fluconazole is limited by lack of activity against molds.

Invasive aspergillosis and less common molds, including zygomycetes, Fusarium species, and Scedosporium species, have become increasingly more important causes of IFI-related mortality relative to invasive candidiasis in patients with leukemia and allogeneic HSCT recipients. Some centers have noted an increased frequency of zygomycosis (in the clinic, the terms zygomycosis and mucormycosis are often used synonymously) in patients receiving prophylactic voriconazole. Whether a causal relationship exists or an increased number of highly immunocompromised patients are being treated for relapsed leukemia and second transplants who are at high risk for mold infections is controversial.

When fluconazole and conventional amphotericin B were the principal systemic antifungal agents...
used in patients with cancer, a trade-off existed; amphotericin B had a broader spectrum of antifungal activity but also substantial toxicity. Prophylactic use of long-term amphotericin B during a high-risk period (e.g., neutropenia after chemotherapy for acute leukemia) would expose patients to a toxic drug from which only a minority would derive benefit. A widely adopted alternative approach involved using fluconazole initially as prophylaxis and reserving amphotericin B for empiric therapy in patients with persistent neutropenic fever of unknown origin. The availability of newer broad-spectrum antifungal agents that are less toxic than amphotericin B raised questions as to whether this approach is optimal. Specifically, should mold-active agents be used early in patients who are specified as high risk rather than later as empiric antifungal therapy? If mold-active prophylaxis is used, the authors have argued that little rationale exists to modify the antifungal regimen empirically based on neutropenic fever without physical examination or chest CT findings suggesting an IFI, or positive laboratory markers.

Two prophylactic trials compared fluconazole with itraconazole in allogeneic HSCT recipients from the conditioning regimen through at least the first 100 days, corresponding to the period of acute GVHD.\textsuperscript{43,44} Itraconazole was associated with fewer cases of invasive aspergillosis, but overall survival was similar.\textsuperscript{43,44} Hepatic toxicity and discontinuation because of gastrointestinal intolerance were more common in patients receiving itraconazole.\textsuperscript{43} Itraconazole led to an increase in cyclophosphamide metabolites, which were associated with hyperbilirubinemia and nephrotoxicity during the early transplantation period.\textsuperscript{43} This finding reinforces a note of caution for itraconazole and possibly newer second-generation triazoles, which are potent inhibitors of cytochrome P450 isozymes, about the potential for drug-drug interactions.

Echinocandins are active against Candida and Aspergillus species but not other mold pathogens. In a prophylactic trial comparing miconafungin with fluconazole in autologous and allogeneic HSCT recipients, success required the absence of suspected, proven, or probable IFI through the end of therapy.\textsuperscript{46} Empiric modification of antifungal therapy based on neutropenic fever was equated with a suspected IFI. The frequency of breakthrough candidemia was similar in both arms. Patients receiving miconafungin had fewer cases of invasive aspergillosis than fluconazole recipients, but this difference did not reach statistical significance. Because of the low frequency of breakthrough IFIs in both arms, detecting a benefit of miconafungin over fluconazole was difficult. The superiority of miconafungin was principally driven by a lower frequency of persisting neutropenic fever requiring empiric modification of the antifungal regimen rather than a reduction in documented IFIs.

Posaconazole is an oral azole with activity against the major pathogenic fungi in vitro and in animal models. Posaconazole has been effective as salvage therapy in patients with a broad range of IFIs, including aspergillosis and zygomycosis, and rarer molds.\textsuperscript{47–51} Posaconazole was effective as primary therapy for mucosal candidiasis\textsuperscript{47} but has not been evaluated as primary therapy for IFIs. In patients with myelodysplastic syndrome or acute myelogenous leukemia with prolonged chemotherapy-induced neutropenia, posaconazole was compared with fluconazole or itraconazole (with most patients in the comparator arm receiving fluconazole) as prophylaxis.\textsuperscript{52} Proven or probable IFIs occurred in 7 patients (2%) in the posaconazole group and 25 patients (8%) in the fluconazole or itraconazole group (P < .001). Significantly fewer patients in the posaconazole group had invasive aspergillosis. Survival was improved in posaconazole recipients (P = .04). Serious adverse events possibly related to treatment occurred in 6% of patients in the posaconazole group and in 2% in the fluconazole or itraconazole group (P = .01); the most common treatment-related adverse events were gastrointestinal. Because this was an open-label trial, attribution of drug-related toxicity is subject to potential investigator bias. Although the increased incidence of serious adverse events in patients receiving posaconazole is an important consideration, the benefit of posaconazole for preventing IFIs and increasing overall survival favors its early use as prophylaxis in this patient population.

Another prophylactic trial compared posaconazole with fluconazole in allogeneic HSCT recipients with significant GVHD.\textsuperscript{52} The inclusion criteria included grade II to IV GVHD, chronic extensive GVHD, or intensive immunosuppressive therapy consisting of either high-dose corticosteroids, antithymocyte globulin, or a combination of 2 or more immunosuppressive agents or types of treatment. To the authors’ knowledge, this is the only randomized prophylactic antifungal trial that focused exclusively
on GVHD. Posaconazole was at least as effective as fluconazole in preventing IFIs during the prespecified period of observation (incidence, 5.3% vs. 9.0%, respectively; \( P = .07 \)) but was superior in preventing invasive aspergillosis and deaths caused by IFIs. If the analysis were restricted to the period in which patients received the study drug, posaconazole was superior to fluconazole in preventing IFIs (incidence, 2.4% vs. 7.6%; \( P = .004 \)), particularly invasive aspergillosis (incidence, 1.0% vs. 5.9%; \( P = .001 \)). Treatment-related adverse events were similar between the groups.

These studies establish a new standard of care for mold-active prophylaxis in these specific patient groups. However, limitations are associated with posaconazole use. An increased frequency of serious adverse events occurred in patients receiving posaconazole versus the comparator group in the prophylactic trial involving neutropenic patients (see earlier discussion). Currently, posaconazole is only available as an oral formulation and should be administered with food for optimal bioavailability. Food increased the oral bioavailability of posaconazole by 400% in healthy volunteers. If breakthrough aspergillosis occurs in a patient receiving posaconazole as prophylaxis, what constitutes optimal therapy is unclear. Switching to either voriconazole plus an echinocandin or a lipid formulation of amphotericin B plus an echinocandin is a reasonable approach in the absence of adequate clinical data. Testing of serum posaconazole levels is limited by large interindividual variability and the lack of well-defined target levels, but can be considered in cases of breakthrough fungal disease. Finally, although no evidence shows that posaconazole prophylaxis selects for resistant fungal pathogens, this scenario is a potential future concern about Candida species that are endogenous flora. Because molds are ubiquitous in the environment and are not endogenous flora, posaconazole or other mold-active azoles would unlikely “select” for resistant opportunistic molds.

Is it possible to provide even better than a strategy of posaconazole prophylaxis for all patients at high risk? Because approximately 10% or less of fluconazole recipients developed an IFI in both trials, can yeast-active prophylaxis with fluconazole be used in most patients and a combination of chest CT scans and surveillance laboratory markers be used to target specific patients for mold-active agents? The preemptive approach has been cogently supported by experienced and respected investigators. Studies comparing competing diagnostic and treatment algorithms (e.g., prophylactic vs. preemptive) rather than simply one drug with another are required to delineate optimal strategies tailored to specific patient populations. Definitive trials of preemptive strategies should be randomized and have the goal of showing a morbidity or mortality gain over standard approaches. Is sufficient evidence currently available showing that the net benefit of the preemptive approach is at least on par with posaconazole prophylaxis in the specific patient groups that were studied?

Preemptive Antifungal Therapy: Progress and Gaps in Knowledge

An important distinction exists between preemptive antifungal therapy and preemptive therapy against cytomegalovirus (CMV) disease. Preemptive antiviral therapy based on surveillance antigen or polymerase chain reaction detection has become standard for preventing CMV disease in allogeneic HSCT recipients. Preemptive CMV therapy relies on detecting viral replication to stratify the risk for developing CMV disease. A positive result from CMV surveillance testing triggers preemptive antiviral therapy to prevent CMV disease. In contrast, preemptive antifungal strategies currently rely on laboratory markers, radiologic monitoring, or both to identify early IFIs before clinically overt disease develops. Thus, CMV viremia precedes viral organ disease (e.g., pneumonia, colitis), whereas fungal disease (which may be microscopic) precedes fungal antigenemia. The preemptive antifungal approach is designed not to treat patients at high risk for an IFI, but rather to initiate early therapy in those with possible early fungal disease; it should therefore be regarded as an early treatment approach rather than a prevention strategy.

To the authors’ knowledge, peer-reviewed publication on preemptive antifungal therapy is limited to one feasibility study. A total of 136 treatment episodes for patients with neutropenia at high risk for IFI were screened with daily serum galactomannan testing. A diagnostic evaluation, which included chest CT scans and bronchoalveolar lavage, was incorporated into the diagnostic algorithm. Only patients who met prespecified criteria for probable or proven invasive fungal infection received liposomal amphotericin B;
neutropenic fever alone did not trigger modification in the antifungal regimen. Although this approach was successful in identifying early invasive aspergillosis and avoiding amphoterin B use in most patients with persistent neutropenic fever of unknown origin, the frequency of invasive aspergillosis was fairly high. It developed in 17 patients and zygomycosis in 1 patient among 136 chemotherapy treatment episodes. All cases of invasive aspergillosis were identified through positive antigenemia results. Seven (41%) deaths occurred in patients with positive serum galactomannan results; of these, 6 had autopsy-proven invasive aspergillosis. However, only 2 patients were considered to have died directly because of invasive aspergillosis.

The authors would add a note of caution about attribution of mortality. No standardized criteria distinguish death with invasive aspergillosis from death caused by invasive aspergillosis. The low autopsy rate in clinical trials adds another level of uncertainty to attributing mortality. Invasive aspergillosis and other IFIs can cause mortality in ways that are not obvious and may not be detectable within a short observation period. For example, a diagnosis of invasive aspergillosis may delay antineoplastic therapy or HSCT, which may then increase the likelihood of relapse of malignancy.

A randomized double-blinded trial comparing fluconazole with voriconazole as prophylaxis after standard-risk myeloablative allogeneic HSCT incorporated key elements of preemptive antifungal therapy. The study encompassed both the early neutropenic period and the later transplantation period when GVHD occurs. Incorporation of real-time serum galactomannan monitoring enabled early detection of invasive aspergillosis and modification of the antifungal regimen. Seen in this light, the protocol compared anti- mold prophylaxis (voriconazole) with a strategy of yeast-active prophylaxis (fluconazole) coupled with galactomannan monitoring and early switch to a mold-active regimen if prespecified criteria were met. No difference was seen between the study arms in fungal-free survival, which was the primary end point of the study, or in overall survival. These results were published in abstract form.

An important consideration when analyzing these data relates to the proportion of patients with significant GVHD requiring intensive immunosuppressive therapy. Although the posaconazole versus fluconazole prophylactic trial in allogeneic HSCT recipients focused on patients with severe GVHD, the voriconazole versus fluconazole prophylactic trial enrolled patients at different risk for GVHD and excluded patients who received allografts with significant human leukocyte antigen (HLA) disparity (< 5 of 6 HLA match) who were at highest risk for severe GVHD.

The strategy of yeast-active prophylaxis with galactomannan monitoring may be optimal for patients at intermediate risk for invasive aspergillosis, whereas mold-active prophylaxis may be optimal for patients at highest risk. Figure 1 summarizes some variables that may favor a preemptive versus prophylactic approach. This figure is conceptual, and data from randomized studies comparing competing strategies are required to delineate optimal prevention and early treatment strategies.
Conclusions

Developing prevention and early treatment strategies that maximize benefit and limit toxicity is a high priority. Posaconazole was highly effective as prophylaxis in neutropenic patients with myelodysplastic syndromes and acute myelogenous leukemia and in allogeneic HSCT recipients with significant GVHD. The overall survival benefit of posaconazole versus comparator agents among patients with neutropenia is particularly persuasive. Targeting mold-active antifungal agents to only those who would derive benefit is an important goal of the preemptive antifungal strategy. However, the clinical database supporting the preemptive strategy is at an exploratory level, and important concerns exist about the high incidence of invasive aspergillosis in a feasibility trial evaluating preemptive antifungal therapy. This brings up a question initially raised: does sufficient evidence currently exist that the net benefit of the preemptive approach is at least on par with posaconazole prophylaxis in the specific patient groups studied? The authors believe the answer is no, and that more data are needed evaluating the preemptive strategy. A definitive trial would compare mold-active prophylaxis with a strategy of preemptive therapy in patients at high risk.

References