Prevention and Early Treatment of Invasive Fungal Infection in Patients with Cancer and Neutropenia and in Stem Cell Transplant Recipients in the Era of Newer Broad-Spectrum Antifungal Agents and Diagnostic Adjuncts

Brahm H. Segal,[1,2] Nikolaos G. Almyroudis,[1] Minoo Battiwalla,[1,2] Raoul Herbrecht,[6] John R. Perfect,[3] Thomas J. Walsh,[4] and John R. Wingard[5]

Departments of [1]Medicine and [2]Immunology, Roswell Park Cancer Institute, Buffalo, New York; [3]Department of Medicine, Duke University Medical Center, Durham, North Carolina; [4]Immunocompromised Host Section, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; [5]Department of Medicine, University of Florida Shands Cancer Center, Division of Hematology/Oncology, Gainesville, Florida; and [6]Hematology and Oncology Department, University Hospital of Strasbourg, Strasbourg, France

Invasive fungal infection (IFI) is a leading cause of infection-related mortality among patients with cancer and prolonged neutropenia and among allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Invasive candidiasis was the principal IFI in the period predating fluconazole prophylaxis, whereas today, invasive aspergillosis and other mold infections cause the majority of deaths from fungal infection in this patient population. The changing epidemiology of IFI, in addition to advances made in antifungal therapeutics and early diagnosis of IFI, warrant a reevaluation of earlier strategies aimed at prevention and early treatment of IFI that were developed several years ago. Here, we propose that persistent neutropenic fever is nonspecific for an IFI and should not be used as the sole criterion for empirical modification in the antifungal regimen in a patient receiving mold-active prophylaxis. We explore the potential benefits and gaps in knowledge associated with employing chest CT scans and laboratory markers as diagnostic adjuncts for IFI. Finally, we discuss the implications of newer antifungal agents and diagnostic adjuncts in the design of future clinical trials to evaluate prophylaxis and early prevention strategies.

Invasive fungal infection (IFI) is a major cause of morbidity and mortality among patients with acute leukemia and receipt of an allogeneic hematopoietic stem cell transplant (HSCT). Four strategies for prevention and treatment of IFI include (1) prophylaxis, (2) empirical antifungal therapy, (3) preemptive antifungal therapy, and (4) treatment of established fungal infection (table 1). Even among highly immunocompromised patients, most will not develop an IFI. Therefore, any prevention strategy entails administering an antifungal agent to a prespecified patient population in which only a minority would be expected to benefit (table 2).

Prophylactic fluconazole has led to a decrease in the frequency of invasive candidiasis among patients with leukemia and among HSCT recipients. However, invasive aspergillosis (IA) [1–3] and less common molds, including zygomycetes [4], *Fusarium* species, [5–7], and *Scedosporium* species, have become increasingly important causes of IFI-related mortality relative to invasive candidiasis among patients with leukemia and among allogeneic HSCT recipients [3, 8, 9]. Some centers have noted an increased frequency of zygomycosis in patients receiving prophylactic voriconazole [10–12]; it is controversial whether a causal relationship exists or whether this finding reflects a larger pool of highly immunocompromised patients. Modern prophylactic and early-treatment strategies are required that encompass the changing epidemiology of IFI, advances in antifungal agents, and improved diagnostic tools (e.g., chest CT scans and laboratory markers) that facilitate early detection of IFI.

Empirical antifungal therapy for neutropenic fever has been studied in >3000 patients and has been codified in authoritative guidelines [13, 14]. Its use was justifiably supported because of the combination of inadequate diagnostic testing, the need for early antifungal drug treat-

Received 12 July 2006; accepted 4 October 2006; electronically published 2 January 2007.

Reprints and correspondence: Dr. Brahm H. Segal, Div. of Infectious Diseases, Roswell Park Cancer Institute, Elm and Carlton Sts., Buffalo, NY 14263 (brahm.segal@roswellpark.org).

Clinical Infectious Diseases 2007; 44:402–9

1058-4838/2007/4403-0015$15.00

ment of IFI, uncertain prophylactic regimens, and high-level morbidity and mortality from IFI.

Although fever in a neutropenic patient should prompt a meticulous evaluation, we challenge the principle of using fever alone as a specific entry point for clinical decisions regarding patients receiving mold-active prophylaxis when we have diagnostic tools that allow us to make a more precise diagnosis. Challenges and pitfalls in prevention trials involving non-neutropenic allogeneic HSCT recipients at high risk for IFI are discussed. We also discuss significant gaps in knowledge that may be the basis for future clinical trials.

HISTORICAL PERSPECTIVE

In the 1960s and 1970s, the development of antipseudomonal β-lactams and the routine use of empirical antibacterial therapy at the onset of neutropenic fever reduced mortality from bacterial infections [15]. More patients were treated with potent cytotoxic regimens (e.g., for acute leukemia), and IFI became a frequent cause of mortality in these patients. Before the use of empirical antifungal therapy, IFIs were frequently diagnosed at autopsy in patients with leukemia and unexplained persistent neutropenic fever; *Candida* and *Aspergillus* species were the principal pathogens [16, 17]. Thus, the rationale for empirical antifungal therapy is that clinical examination and cultures are not sufficiently sensitive for early detection of IFI and that early treatment of IFI can be life saving [18].

Two randomized prospective studies in the 1980s showed that empirical amphotericin B deoxycholate (AmB-D) was associated with a trend toward fewer IFIs in antibiotic-treated neutropenic patients with persistent fever [16, 19]. In the larger study, no deaths from IFI occurred in patients receiving empirical AmB-D, compared with 4 deaths from IFI in the control group ($P = .05$). The benefit of empirical AmB-D therapy primarily occurred in patients who did not receive antifungal prophylaxis [19]. Because both studies were underpowered and neither showed a statistically significant benefit of empirical antifungal therapy in preventing IFIs or overall mortality, some investigators argue that a placebo arm in empirical antifungal therapy studies could be justified in future trials, particularly if prophylaxis against candidiasis were included [20].

FLUCONAZOLE VERSUS AMPHOTERICIN B (EARLY VS. LATE) PARADIGM

Because of its toxicity, AmB-D was more likely to be used as empirical therapy for neutropenic fever than as prophylaxis, which would entail treating a larger number of patients over a longer period [21]. Fluconazole therapy is effective in preventing invasive candidiasis in HSCT recipients [22–24], although breakthrough fluconazole-sensitive and fluconazole-resistant infections occur [25]. A meta-analysis of randomized studies of azole prophylaxis (fluconazole, ketoconazole, miconazole, and itraconazole) in neutropenic patients demonstrated that azoles led to reductions in the use of parenteral antifungal therapy, superficial fungal infections, IFIs, and fungal infection–related mortality [26]. The incidence of IA was unaffected. In a meta-analysis of 16 randomized, controlled trials involving patients who did not receive HSCT and who had chemotherapy-induced neutropenia, fluconazole prophylaxis was beneficial when the incidence of IFI was expected to be >15% [27].

Empirical therapy for neutropenic fever initially involved initiation of AmB-D therapy to increase the spectrum of activity to include molds and azole-resistant *Candida* species. The trade-off was straightforward: early administration of a narrow-spectrum but safe agent (fluconazole), compared with later administration of a broader spectrum agent with greater toxicity (AmB-D).

There are many causes of fever in neutropenic patients (e.g., bacterial infections, transfusion reactions, drug reactions, tissue necrosis, and growth factors). IFIs are documented in ⩽5% of patients enrolled in modern empirical antifungal trials in which antifungal prophylaxis was commonly used [28–31]. Indeed, 2 randomized trials showed that fluconazole was equally effective but safer than AmB-D as empirical therapy for persistently febrile

Table 1. Strategies for prevention and treatment of invasive fungal infection (IFI).

Strategy	Definition
Prophylaxis	Administration of the antifungal agent is initiated at a period of high risk of infection to prevent fungal infections
Empirical treatment	Initiation or modification of an existing antifungal regimen in persistently febrile patients with neutropenia (generally 4–7 days in duration) that is without a known source and is unresponsive to appropriate antibacterial agents
Preemptive therapy	Similar to empirical antifungal therapy, preemptive therapy aims to treat a suspected early IFI but uses radiologic studies, laboratory markers, or both (rather than fever alone) to stratify the likelihood of an IFI[a]; meeting prespecified criteria would trigger preemptive initiation or modification of antifungal therapy
Treatment of established IFI	Corresponds to patients who meet European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria for proven and probable IFI [71]

[a] Standardized definitions for what constitutes preemptive antifungal therapy are required. For example, a positive serum galactomannan or β-glucan assay result for a neutropenic patient with persistent fever may be used as a trigger to modify the antifungal regimen in a preemptive strategy. Another preemptive strategy may use chest CT findings as a decision node regarding modification of the antifungal regimen. Other preemptive strategies may use laboratory and radiologic studies in different sequences. Triggers for preemptive antifungal therapy must be distinguished from a "probable IFI," as defined by European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria; antifungal therapy in this situation is aimed at treating a documented IFI rather than at being preemptive.

Table 2. Premises for prophylactic and early-treatment strategies.

Premise
The more dangerous the infection, the greater the need for effective prophylaxis or early-intervention strategies. Conversely, prophylaxis is not warranted for infections that are not serious or that easily respond to therapy.
The higher the incidence of infection within a given population, the more likely we are to use a prevention or early-treatment strategy.
The safer the antifungal agent, the more likely we are to use it in a large number of patients (e.g., as prophylaxis) in which only a minority would be expected to benefit but in which very few would incur toxicity.
The better the methods for early detection of occult fungal infection, the more willing we are to withhold antifungal prophylaxis or to not modify the antifungal regimen for patients with negative screening results.
Although it is not the primary consideration, the cost of an antifungal agent and the cost of screening strategies may have an effect on how they are used.

neutropenic patients [32, 33]. Because of its lack of activity against molds, the authors cautioned that chest radiographs or CT scans be performed prior to initiating empirical fluconazole therapy [32].

NEWER ANTIFUNGAL AGENTS

The development of newer antifungal agents with activity against yeasts and molds and with superior safety and tolerability, compared with AmB-D, raised questions about whether the older paradigm of early and safe treatment versus late and potentially toxic treatment should be continued [34]. The improved tolerability of lipid formulations of amphotericin B, azoles, and echinocandins, compared with AmB-D, has prompted many centers to use these agents early, as prophylaxis, rather than later, as empirical therapy for neutropenic fever [14, 35, 36].

Indeed, it is common for agents within the same class and with a similar spectrum to be evaluated as prophylaxis and as empirical therapy in separate trials. The echinocandins provide an instructive example. Caspofungin was at least as effective as and less toxic than liposomal amphotericin B as empirical therapy in persistently febrile patients with neutropenia [30]. The success rate in each arm, using a prespecified composite outcome, was only 34%, with the majority of treatment failures being driven by a lack of resolution of fever during the neutropenic period. In a prophylactic trial of autologous and allogeneic HSCT recipients that compared micafungin with fluconazole, treatment success required the absence of suspected, probable, or proven IFI through the end of therapy [36]. Empirical modification of antifungal therapy on the basis of neutropenic fever was equated with a suspected IFI. The frequency of breakthrough candidemia was similar in both arms, but there was a trend to fewer episodes of IA in allogeneic HSCT recipients receiving micafungin. The superiority of micafungin therapy was principally driven by a lower frequency of persistent neutropenic fever requiring empirical modification of the antifungal regimen.

These trials raise 2 questions. First, should persistent fever without evidence of a breakthrough IFI be a criterion for failure in antifungal prophylactic and empirical trials? Several empirical antifungal studies have employed a composite outcome in which fulfillment of several prespecified criteria were required for a successful outcome [29–31]. These composite outcomes have generally included the following: (1) absence of breakthrough fungal infections, (2) successful treatment of baseline fungal infections, (3) survival, (4) no premature study withdrawal, and (5) resolution of fever during neutropenia.

In studies comparing voriconazole with liposomal amphotericin B and caspofun-

Table 3. Primary end points for prevention and early treatment antifungal trials.

Aim of trial	Primary end points for successful outcome
Prophylaxis	Survival;[a] absence of proven or probable breakthrough IFI;[b] and premature withdrawal as a result of study drug toxicity[c]
Empirical antifungal therapy[d]	Survival; absence of proven or probable breakthrough IFI; successful treatment of any baseline IFI; and no premature withdrawal as a result of study drug toxicity
Preemptive antifungal therapy[e]	Same end points as empirical antifungal therapy

NOTE. IFI, invasive fungal infection.

[a] We believe that overall survival is a preferable criterion, compared with absence of mortality attributable to an IFI, for 2 reasons. First, attribution of mortality, especially without autopsy data, is difficult. Second, drug toxicity may influence survival in ways that are not obvious to the investigator (e.g., a drug-drug interaction).

[b] Proven and probable IFIs are defined per European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria [71]. Possible IFIs should not be included as criteria for prophylaxis failure.

[c] Protocols should prespecify criteria for modification of the prophylactic antifungal regimen and should generally be restricted to a proven or probable breakthrough IFI or significant drug toxicity (e.g., National Cancer Institute common toxicity criteria of grade 3 or higher). Some investigators may reasonably argue that drug toxicity that is significant but easily reversible with drug cessation (e.g., gastrointestinal intolerance) should not per se be equated with prophylaxis failure. Other reasons for premature drug discontinuation (e.g., persistent neutropenic fever or patient noncompliance) should not be equated with prophylactic failure.

[d] We question the value of conducting further trials of empirical antifungal therapy in which persistent fever of unknown etiology is the sole trigger for modifying the antifungal regimen in neutropenic patients receiving mold-active prophylaxis.

[e] Rather than compare one drug with another, a preemptive trial may involve comparing 2 different diagnostic and treatment algorithms.

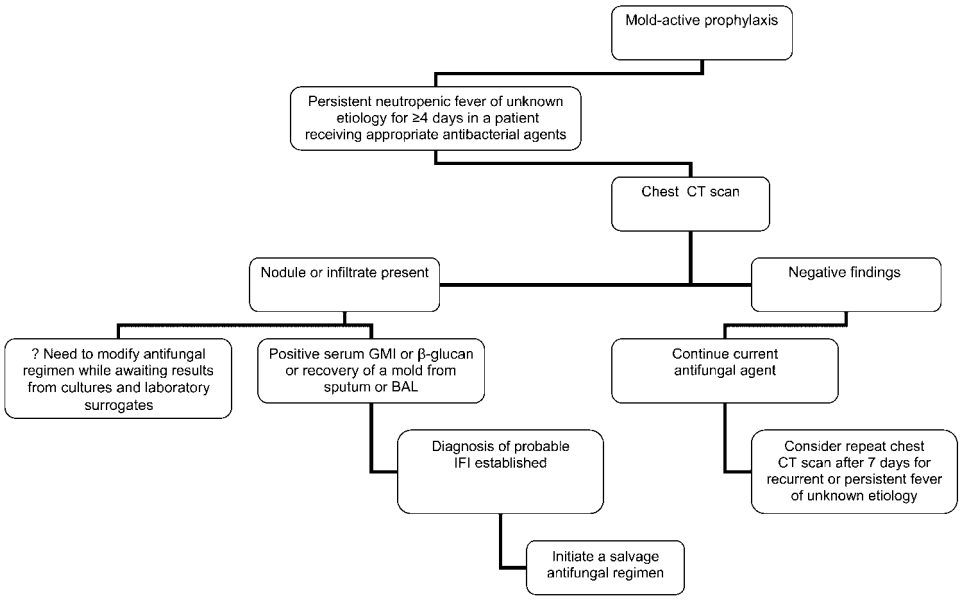

Figure 1. Proposed algorithm for early diagnosis of invasive fungal infection (IFI) and use of antifungal regimens in neutropenic patients with persistent fever of unknown etiology. When mold-active prophylaxis is used, we propose an algorithm in which the initial prophylactic agent is continued with negative diagnostic results. Although this algorithm addresses neutropenic patients, the concepts are applicable to other patients at high risk for IFIs (e.g., allogeneic hematopoietic stem cell transplant recipients). BAL, bronchoalveolar lavage fluid; GMI, galactomannan index.

gin with liposomal amphotericin B, the proportion of patients with a successful outcome in the different treatment arms was 26%–34% [29, 30]. However, the proportion of patients with breakthrough IFIs, poorly controlled baseline IFIs, or mortality was relatively small. The most common reason for treatment failure was lack of resolution of fever during neutropenia. The rationale for including fever resolution as a criterion for a successful outcome is that this is precisely the trigger used to initiate empirical antifungal therapy. However, fever is neither a sensitive nor a specific sign of an IFI. Fever resolution was the least clinically meaningful end point in the composite outcome, and yet it accounted for most of the treatment failures, with the potential to mask more-relevant clinical outcomes [37]. Therefore, we suggest that modification of the antifungal regimen solely on the basis of persistent neutropenic fever should not be equated with treatment failure in either prophylactic or empirical antifungal studies (table 3).

The second question relates to whether empirical modification of the antifungal regimen is warranted solely on the basis of persistent neutropenic fever in patients receiving mold-active prophylaxis. No studies specifically address this question. This question has become particularly relevant in light of recent data on posaconazole prophylaxis. Posaconazole has activity in vitro and in animal models against the major pathogenic fungi [38–42]. Posaconazole has been effective as salvage therapy in patients with a broad range of IFIs [41, 43–47]. Posaconazole was effective as primary therapy for mucosal candidiasis [48], but it has not been evaluated as primary therapy for IFI. Prophylaxis with posaconazole led to fewer IFIs and less overall mortality, compared with prophylaxis with fluconazole or itraconazole, in neutropenic patients with acute leukemia or myelodysplastic syndrome in a randomized trial [49]. Results of this trial have been reported in abstract form and require confirmation by peer review. The availability of effective and safe mold-active prophylaxis creates the need for a new paradigm to diagnose breakthrough IFIs early and to modify the antifungal regimen in only those patients who meet prespecified criteria.

ALLOGENEIC HSCT

Several studies have reported the predominance of aspergillosis cases occurring in the postengraftment period, rather than in the neutropenic period, among allogeneic HSCT recipients [2, 50–56], with immunosuppressive therapy for graft-versus-host disease (GVHD) and T cell depletion being principal risk factors. Marr et al. [3] noted an increased incidence of infections due to less common fungal pathogens, including zygomycetes and *Fusarium* and *Scedosporium* species, among allogeneic HSCT recipients—particularly among patients with multiple stem cell transplants for relapsed malignancy, who are among the most severely immunocompromised HSCT recipients. In contrast to neutropenic patients, patients with GVHD who are receiving corticosteroids and other immunosuppressive agents commonly do not experience fever during IFI [56].

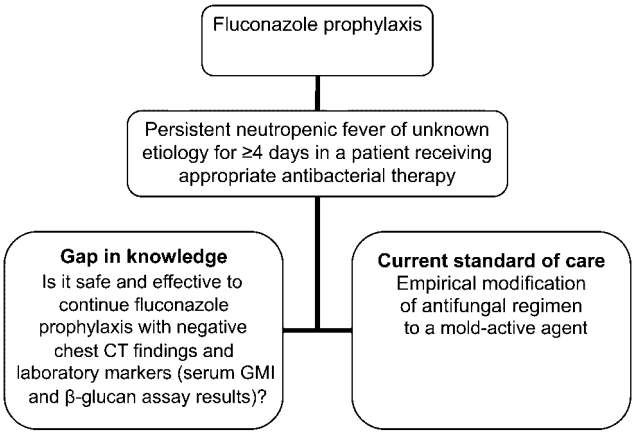

Figure 2. Proposed algorithm for early diagnosis of invasive fungal infection (IFI) and use of antifungal regimens in neutropenic patients with persistent fever of unknown etiology. When prophylaxis with fluconazole is used, empirical antifungal therapy in neutropenic patients with persistent fever is likely to benefit the small minority of patients with an occult IFI. Whether fluconazole prophylaxis can be safely continued in a subset of patients with negative radiologic findings and negative laboratory results is an unanswered question. GMI, galactomannan index.

Until recently, almost all clinical trials of antifungal prophylaxis in patients with cancer focused on neutropenic patients. Two prophylactic trials comparing fluconazole with itraconazole have addressed this changing epidemiology by extending the period of administration of antifungal drugs from the time of the conditioning regimen through at least the first 100 days, corresponding to the period of acute GVHD [57, 58]. Itraconazole prophylaxis was associated with fewer cases of IA, but overall survival rates were similar [57, 58]. Hepatic toxicity and discontinuation of prophylaxis because of gastrointestinal intolerance were more common in itraconazole recipients [57]. Itraconazole led to an increase in cyclophosphamide metabolites, which, in turn, were associated with hyperbilirubinemia and nephrotoxicity during the early posttransplantation period [59]. This finding reinforces a note of caution about itraconazole and newer second-generation triazoles, which are potent inhibitors of cytochrome P450 isoenzymes, regarding the potential for drug-drug interactions.

Posaconazole was compared with fluconazole as prophylaxis in allogeneic HSCT recipients with significant GVHD in a prospective, randomized, double-blinded study [60]. Posaconazole prophylaxis led to reductions in the incidence of IA, the total number of IFIs experienced while receiving treatment, and the number of deaths attributed to fungal infection. These results have been reported in abstract from and require confirmation by peer review. If posaconazole is used in allogeneic HSCT recipients with GVHD, breakthrough IFIs would be expected to be uncommon, and conceivably, the proportion of infections due to uncommon drug-resistant pathogens (e.g., *Scedosporium* species) or azole-resistant yeasts might increase. Development of effective surveillance strategies for use in this patient population that have a high positive predictive value (PPV), to detect breakthrough IFIs early, and a high negative predictive value (NPV), to avoid unnecessary modifications in antifungal prophylaxis, pose an important challenge for future research.

NEED FOR VALIDATED SURROGATE MARKERS

Both the serum *Aspergillus* galactomannan and β-glucan assays have been accepted as diagnostic adjuncts of IFI in the revised European Organization for Research and Treatment of Cancer/Mycosis Study Group consensus criteria (which is currently in preparation). PCR-based detection is considered to be investigational.

These markers have advantages and limitations. Several variables can affect the performance of the galactomannan assay [61, 62] and may account for differences in the results of prospective studies. The sensitivity of the assay is reduced by concomitant mold-active antifungal agents [63, 64]. False-positive results may be more common among children and allogeneic HSCT recipients [65]. Receipt of concomitant piperacillin-tazobactam can cause false-positive galactomannan assay results [66, 67].

Herbrecht et al. [65] evaluated galactomannan antigenemia in patients at risk for IA. The sensitivity of the assay was 64.5% for cases of definite IA. The PPV of the test varied among different patient groups, and the lowest PPVs occurred when the test was used as a surveillance tool among patients with persistent neutropenic fever (PPV, 7.1%) and in HSCT recipients (PPV, 10%); the NPV was 100% in both groups. A recent meta-analysis showed that the galactomannan assay had a sensitivity of 70% and a specificity of 89% for proven IA and that the accuracy of the test was variable among different patient populations [68]. In populations with a prevalence of IA of 5%–10%, the expected PPV was 23%–53%, whereas the expected NPV was 95%–99% [68].

Detection of β-glucan has received US Food and Drug Administration approval for use for presumptive diagnosis of IFI. Among patients with acute myeloid leukemia and myelodysplastic syndrome, the assay was highly sensitive and specific in detecting early IFIs, including candidiasis, fusariosis, trichosporonosis, and aspergillosis [69]. The NPV was 100%. Experience with use of the β-glucan assay in HSCT recipients is limited [70], and the use of this assay in this population requires additional study.

Although valuable as diagnostic adjuncts to support a diagnosis of a probable

IFI in patients with compatible host factors and radiological findings as defined in the European Organization for Research and Treatment of Cancer/Mycosis Study Group criteria [71], the value of these laboratory markers as screening tools for IFIs is controversial, and more research is required. In neutropenic patients with fever without localizing symptoms or physical examination findings who have negative blood culture results and negative chest CT findings, a negative galactomannan and/or β-glucan assay result lends additional support for the absence of a breakthrough IFI.

INCORPORATION OF CT SCANS AND LABORATORY DETECTION MARKERS INTO MANAGEMENT ALGORITHMS: GAPS IN KNOWLEDGE

Preemptive antiviral therapy on the basis of surveillance-antigen or PCR detection has become standard for preventing cytomegalovirus disease in allogeneic HSCT recipients [72]. Preemptive antifungal strategies are at an exploratory level and do not have standardized criteria. Laboratory markers, radiological monitoring, or both are used to identify early IFIs before the development of clinically overt disease. This approach differs from preemptive cytomegalovirus therapy, which relies on the detection of viral replication to stratify the risk for developing cytomegalovirus disease.

In an open-label feasibility study, Maertens et al. [73] used serial serum galactomannan and chest CT scanning to detect early aspergillosis in high-risk neutropenic patients receiving fluconazole prophylaxis. This strategy reduced the use of empirical antifungal therapy and successfully identified cases of early IA, but it may not be adequate to identify early infection with non-*Aspergillus* molds.

An ongoing randomized double-blind trial comparing fluconazole with voriconazole as prophylaxis after allogeneic HSCT incorporates some of the elements of preemptive antifungal therapy. The study encompasses both the early neutropenic period and the later posttransplantation period when GVHD occurs. Incorporation of real time serum galactomannan monitoring aims to permit early detection of IA and modification of the antifungal regimen. Seen in this light, the protocol compares antimold prophylaxis (voriconazole) with the strategy of using a narrower spectrum agent (fluconazole) coupled with galactomannan monitoring and an early switch to a mold-active regimen if prespecified criteria are met [74]. Because the potential benefit of prophylactic voriconazole may be offset by increased toxicity, equipoise exists [74]. In a manner similar to that used in trials of itraconazole prophylaxis, the use of empirical antifungal therapy with amphotericin B for persistent neutropenic fever of unknown etiology was not scored as failure of prophylaxis [57, 58].

Because no study has evaluated empirical modification of antifungal therapy in neutropenic patients receiving mold-active prophylaxis on the basis of persistent fever alone, we propose an algorithm in which the initial prophylactic agent is continued with negative diagnostic results (figure 1). In this algorithm, fever prompts further evaluation, rather than being an automatic trigger to change the antifungal regimen in the absence of evidence of failure prophylaxis. Testing newer early diagnostic algorithms to detect breakthrough IFIs in high-risk patients receiving mold-active prophylaxis would address an important gap in knowledge.

In patients receiving no antifungal prophylaxis or fluconazole prophylaxis, empirical antifungal trials have shown that a small minority have baseline IFIs at the time of study enrollment. For example, in the empirical antifungal trial comparing caspofungin and liposomal amphotericin B, ~5% of patients in both arms had a baseline IFI (almost 90% of these IFIs were invasive candidiasis or IA) [30]. Empirical antifungal therapy initiated prior to diagnosis of IFI would be expected to benefit this small minority of patients. Empirical treatment with caspofungin is not associated with greater toxicity than fluconazole used as prophylaxis, and it represents a viable strategy. Whether it is safe to continue fluconazole prophylaxis in neutropenic patients with persistent fever of unknown etiology who have negative chest CT findings and negative laboratory markers merits further study (figure 2).

Studies that compare competing diagnostic and treatment algorithms, rather than simply comparing one drug with another, are required to delineate optimal strategies tailored to specific patient populations. Such studies should be randomized and aim to demonstrate an improvement in morbidity or mortality over standard approaches, and they should include an analysis of the cost of competing strategies.

CONCLUSIONS

Three factors create the need to reevaluate older paradigms for prophylaxis and early treatment of suspected IFIs. The first is the change in the epidemiology of IFIs, in which mold infections pose a greater threat than invasive candidiasis in patients with acute leukemia and allogeneic HSCT. Among allogeneic HSCT recipients, the predominance of invasive mold infection during GVHD, rather than neutropenia, has led to recent prophylactic trials that encompass the GVHD period. Second, the availability of effective and safe mold-active agents challenges the older paradigm of using fever alone as a trigger to modify antifungal therapy. Third, chest CT findings and laboratory markers as diagnostic adjuncts for IFI may be useful as triggers to initiate or modify antifungal therapy. It is a high priority to validate the application of these tests to antifungal algorithms.

Acknowledgments

Potential conflicts of interest. B.S. has received speaking honoraria from Merck and Pfizer and has received research funding from Enzon; has been a consultant for Schering-Plough, Pfizer, and Enzon; and was a compensated data-review committee member for Schering-Plough. J.W. has been a consultant and received honoraria from Pfizer and Merck. J.P. has been a consultant and

received research funding and speaking honoraria from Pfizer, Schering-Plough, Merck, Enzon, and Astellas. R.H. has received research funding from Pfizer and has been a consultant for Pfizer, Merck, Gilead, Astellas, Schering-Plough, and Zeneus. All other authors: no conflicts.

References

1. van Burik JH, Leisenring W, Myerson D, et al. The effect of prophylactic fluconazole on the clinical spectrum of fungal diseases in bone marrow transplant recipients with special attention to hepatic candidiasis: an autopsy study of 355 patients. Medicine (Baltimore) **1998**; 77:246–54.
2. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis **1997**; 175:1459–66.
3. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis **2002**; 34:909–17.
4. Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). Haematologica **2006**; 986–9.
5. Nucci M, Marr KA, Queiroz-Telles F, et al. Fusarium infection in hematopoietic stem cell transplant recipients. Clin Infect Dis **2004**; 38: 1237–42.
6. Boutati EI, Anaissie EJ. Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. Blood **1997**; 90:999–1008.
7. Kontoyiannis DP, Bodey GP, Hanna H, et al. Outcome determinants of fusariosis in a tertiary care cancer center: the impact of neutrophil recovery. Leuk Lymphoma **2004**; 45: 139–41.
8. Walsh TJ, Groll A, Hiemenz J, Fleming R, Roilides E, Anaissie E. Infections due to emerging and uncommon medically important fungal pathogens. Clin Microbiol Infect **2004**; 10(Suppl 1):48–66.
9. Jahagirdar BN, Morrison VA. Emerging fungal pathogens in patients with hematologic malignancies and marrow/stem-cell transplant recipients. Semin Respir Infect **2002**; 17: 113–20.
10. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. Clin Infect Dis **2004**; 39:743–6.
11. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med **2004**; 350:950–2.
12. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary care cancer center in the era of *Aspergillus*-active antifungal therapy: a case control observational study of 27 recent cases. J Infect Dis **2005**; 191:1350–60.
13. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis **2002**; 34:730–51.
14. Freifeld AG, Baden LR, Brown AE, et al. Fever and neutropenia. In: National Comprehensive Cancer Network Practice Guidelines in Oncology. Vol 1. **2005**. Available at: http://www.nccn.org. Accessed 10 September 2006.
15. Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med **1971**; 284: 1061–5.
16. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med **1982**; 72:101–11.
17. Chang HY, Rodriguez V, Narboni G, Bodey GP, Luna MA, Freireich EJ. Causes of death in adults with acute leukemia. Medicine (Baltimore) **1976**; 55:259–68.
18. Aisner J, Schimpff SC, Wiernik PH. Treatment of invasive aspergillosis: relation of early diagnosis and treatment to response. Ann Intern Med **1977**; 86:539–43.
19. EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. Am J Med **1989**; 86:668–72.
20. Bennett JE, Powers J, Walsh T, et al. Forum report: issues in clinical trials of empirical antifungal therapy in treating febrile neutropenic patients. Clin Infect Dis **2003**; 36(Suppl 3): S117–22.
21. Bodey GP, Anaissie EJ, Elting LS, Estey E, O'Brien S, Kantarjian H. Antifungal prophylaxis during remission induction therapy for acute leukemia fluconazole versus intravenous amphotericin B. Cancer **1994**; 73:2099–106.
22. Rotstein C, Bow EJ, Laverdiere M, Ioannou S, Carr D, Moghaddam N. Randomized placebo-controlled trial of fluconazole prophylaxis for neutropenic cancer patients: benefit based on purpose and intensity of cytotoxic therapy. The Canadian Fluconazole Prophylaxis Study Group. Clin Infect Dis **1999**; 28: 331–40.
23. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. J Infect Dis **1995**; 171:1545–52.
24. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation [see comments]. N Engl J Med **1992**; 326:845–51.
25. Marr KA, Seidel K, White TC, Bowden RA. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis **2000**; 181:309–16.
26. Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. Cancer **2002**; 94:3230–46.
27. Kanda Y, Yamamoto R, Chizuka A, et al. Prophylactic action of oral fluconazole against fungal infection in neutropenic patients: a meta-analysis of 16 randomized, controlled trials. Cancer **2000**; 89:1611–25.
28. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med **1999**; 340:764–71.
29. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med **2002**; 346:225–34.
30. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med **2004**; 351:1391–402.
31. Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: a randomized, controlled trial. Ann Intern Med **2001**; 135:412–22.
32. Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. Am J Med **2000**; 108:282–9.
33. Viscoli C, Castagnola E, Van Lint MT, et al. Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial. Eur J Cancer **1996**; 32A:814–20.
34. Marr KA. Antifungal therapy for febrile neutropenia: issues in clinical trial design. Curr Opin Investig Drugs **2004**; 5:202–7.
35. Mattiuzzi GN, Kantarjian H, Faderl S, et al. Amphotericin B lipid complex as prophylaxis of invasive fungal infections in patients with acute myelogenous leukemia and myelodysplastic syndrome undergoing induction chemotherapy. Cancer **2004**; 100:581–9.
36. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis **2004**; 39:1407–16.
37. de Pauw BE, Sable CA, Walsh TJ, et al. Impact of alternate definitions of fever resolution on the composite endpoint in clinical trials of empirical antifungal therapy for neutropenic patients with persistent fever: analysis of results from the Caspofungin Empirical Therapy Study. Transpl Infect Dis **2006**; 8:31–7.
38. Pfaller MA, Messer SA, Hollis RJ, Jones RN. In vitro activities of posaconazole (Sch 56592)

compared with those of itraconazole and fluconazole against 3,685 clinical isolates of *Candida* spp. and *Cryptococcus neoformans.* Antimicrob Agents Chemother **2001**; 45:2862–4.
39. Petraitiene R, Petraitis V, Groll AH, et al. Antifungal activity and pharmacokinetics of posaconazole (SCH 56592) in treatment and prevention of experimental invasive pulmonary aspergillosis: correlation with galactomannan antigenemia. Antimicrob Agents Chemother **2001**; 45:857–69.
40. Pfaller MA, Messer SA, Boyken L, Hollis RJ, Diekema DJ. In vitro susceptibility testing of filamentous fungi: comparison of Etest and reference M38-A microdilution methods for determining posaconazole MICs. Diagn Microbiol Infect Dis **2003**; 45:241–4.
41. Torres HA, Hachem RY, Chemaly RF, Kontoyiannis DP, Raad II. Posaconazole: a broad-spectrum triazole antifungal. Lancet Infect Dis **2005**; 5:775–85.
42. Gonzalez GM, Tijerina R, Najvar LK, et al. In vitro and in vivo activities of posaconazole against Coccidioides immitis. Antimicrob Agents Chemother **2002**; 46:1352–6.
43. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis **2007**; 44:2–12.
44. Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system infections. J Antimicrob Chemother **2005**; 56:745–55.
45. Segal BH, Barnhart LA, Anderson VL, Walsh TJ, Malech HL, Holland SM. Posaconazole as salvage therapy in patients with chronic granulomatous disease with invasive filamentous fungal infection. Clin Infect Dis **2005**; 40: 1684–8.
46. Kontoyiannis DP, Hare R, Solomon H, Corrado M, van Burik JA. Posaconazole is highly effective as a second-line agent in zygomycosis: summary of 91 cases [abstract M-974]. In: Program and abstracts of the 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: **2005**.
47. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother **2006**; 50:126–33.
48. Vazquez JA, Skiest DJ, Nieto L, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. Clin Infect Dis **2006**; 42:1179–86.
49. Cornely O, Maertens J, Winston D, et al. Posaconazole vs. standard azole (FLU/ITRA) therapy for prophylaxis of invasive fungal infections (IFIs) among high-risk neutropenic patients: results of a randomized, multicenter trial [abstract 1844]. Blood. **2005**; 106.
50. Baddley JW, Stroud TP, Salzman D, Pappas PG. Invasive mold infections in allogeneic bone marrow transplant recipients. Clin Infect Dis **2001**; 32:1319–24.
51. Grow WB, Moreb JS, Roque D, et al. Late onset of invasive *Aspergillus* infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant **2002**; 29:15–9.
52. Jantunen E, Ruutu P, Niskanen L, et al. Incidence and risk factors for invasive fungal infections in allogeneic BMT recipients. Bone Marrow Transplant **1997**; 19:801–8.
53. McWhinney PH, Kibbler CC, Hamon MD, et al. Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: 13 years' experience. Clin Infect Dis **1993**; 17:397–404.
54. Yuen KY, Woo PC, Ip MS, et al. Stage-specific manifestation of mold infections in bone marrow transplant recipients: risk factors and clinical significance of positive concentrated smears. Clin Infect Dis **1997**; 25:37–42.
55. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood **2002**; 100: 4358–66.
56. Shaukat A, Bakri F, Young P, et al. Invasive filamentous fungal infections in allogeneic hematopoietic stem cell transplant recipients after recovery from neutropenia: clinical, radiologic, and pathologic characteristics. Mycopathologia **2005**; 159:181–8.
57. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fuconazole for prevention of fungal infections in allogeneic stem cell transplant patients. Blood **2003**; 2:2.
58. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients: a multicenter, randomized trial. Ann Intern Med **2003**; 138:705–13.
59. Marr KA, Leisenring W, Crippa F, et al. Cyclophosphamide metabolism is impacted by azole antifungals. Blood **2003**; 22:22.
60. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole (POS) vs. Fluconazole (FLU) for prophylaxis for invasive fungal infections (IFIs) in allogeneic hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD): results of a multicenter trial [abstract M-716]. In: Program and abstracts of the 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: **2005**.
61. Wheat LJ. Rapid diagnosis of invasive aspergillosis by antigen detection. Transpl Infect Dis **2003**; 5:158–66.
62. Mennink-Kersten MA, Donnelly JP, Verweij PE. Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis. Lancet Infect Dis **2004**; 4:349–57.
63. Marr KA, Balajee SA, McLaughlin L, Tabouret M, Bentsen C, Walsh TJ. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. J Infect Dis **2004**; 190:641–9.
64. Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the *Aspergillus* galactomannan enzyme immunoassay. Clin Infect Dis **2005**; 40:1762–9.
65. Herbrecht R, Letscher-Bru V, Oprea C, et al. *Aspergillus* galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. J Clin Oncol **2002**; 20:1898–906.
66. Walsh TJ, Shoham S, Petraitiene R, et al. Detection of galactomannan antigenemia in patients receiving piperacillin-tazobactam and correlations between in vitro, in vivo, and clinical properties of the drug-antigen interaction. J Clin Microbiol **2004**; 42:4744–8.
67. Sulahian A, Touratier S, Ribaud P. False positive test for *Aspergillus* antigenemia related to concomitant administration of piperacillin and tazobactam. N Engl J Med **2003**; 349: 2366–7.
68. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis **2006**; 42:1417–27.
69. Odabasi Z, Mattiuzzi G, Estey E, et al. β-D-glucan as a diagnostic adjunct for invasive fungal infections: validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clin Infect Dis **2004**; 39:199–205.
70. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1–>3) β-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis **2005**; 41:654–9.
71. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis **2002**; 34: 7–14.
72. Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood **2002**; 99:1159–64.
73. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography–based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis **2005**; 41:1242–50.
74. Wingard JR. Design issues in a prospective randomized double-blinded trial of prophylaxis with fluconazole versus voriconazole after allogeneic hematopoietic cell transplantation. Clin Infect Dis **2004**; 39(Suppl 4): S176–80.